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HEART BLOCK DUE TO CALCAREOUS LESIONS OF THE BUNDLE OF HIS

REVIEW AND REPORT OF A CASE WITH DETAILED HISTOPATHOLOGIC STUDY *

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CONSIDERING the fact that only 47 cases of established complete heart block reported in the literature have been sufficiently thoroughly studied to be acceptable as conclusive, we believe that further careful studies of this subject are important. These 47 cases have been tabulated by Yater, Cornell and Claytor.[1] In nine cases the auriculoventricular dissociation was due to calcareous or fibrocalcareous lesions of the bundle of His. Together with fibrosis of the bundle or bundle and branches, fibrosis of the two bundle branches without lesions of the main bundle, and gummatous invasion of the bundle, this type of lesions constituted one of the most common causes of complete heart block.

In order to determine whether the calcific lesions causing heart block possess common characteristics and perhaps similar etiology and pathogenesis, we have carefully reviewed the reports of the nine cases of established complete heart block alluded to and of one case of Yater and Willius [2] of intermittent heart block associated with the same type of lesion. A brief résumé of each of these cases is given below.

1. *Bönninger,*[3] *and Mönckeberg* [4] *(1908).* A man, aged 67 years, had had Adams-Stokes attacks for several years. Toward the end long attacks of asystole occurred, some as long as three minutes, one reported to have lasted eight minutes. The ventricular rate was 30 to 45 per minute. Electrocardiograms (not published) confirmed the complete A–V dissociation. The heart was enlarged. The coronary arteries were not significantly altered. There was severe sclerosis of the aortic and mitral valves, especially the aortic leaflet of the mitral, due to fibrosis and calcification. The latter was most marked in the bottom of the sinuses of Valsalva and at the base of the aortic leaflet of the mitral valve, and extended from both places into the membranous portion of the interventricular septum, which was diffusely thickened. Careful histologic examination showed that the portion of the calcium mass extending from

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the mitral valve completely interrupted the A–V bundle in its midportion. The terminal portion and origins of the bundle branches were normal. The calcium mass was surrounded by dense fibrous tissue containing lymphocytes. Small masses of calcium were present also in the myocardium of the interventricular septum.

2. *Nagayo*[5] *(1909)*. A woman, aged 79 years, had Stokes-Adams attacks for two (?) years before death. Sphygmograms (not published) always showed complete heart block (auricular and ventricular rates not stated). There was severe coronary artery sclerosis. A mass of calcium was imbedded in the upper edge of the myocardium of the interventricular septum at the base of the aortic leaflet of the mitral valve, and there were smaller masses in this valve. Careful histologic examination showed that the main calcium mass strongly compressed the A–V bundle as it traversed the membranous portion of the septum, and in one area completely destroyed it. The bifurcation and upper portions of the bundle branches were normal.

3. *Gibson and Ritchie*[6] *(1909)*. A man, aged 76 years, had Adams-Stokes attacks for three years, during which time the pulse rate was normal except during attacks, when it went as low as 16 per minute. After this, the pulse rate was constantly 28 to 34 per minute, and there were no more attacks in the remaining four years of life. Polygrams (published) showed complete A–V block. The heart was moderately hypertrophied and dilated. The aorta and coronary arteries were dilated. The mitral valve was thickened and calcareous, mainly at the base of the aortic leaflet. The aortic valve was thickened but not deformed. Careful histologic examination showed dense fibrous transformation of the interventricular septum at the juncture of the membranous and muscular portions, with deposits of calcium therein. This fibrocalcareous lesion largely replaced the A–V node and the first portion of the A–V bundle.

4. *Bishop*[7] *(1910), and Oppenheimer and Oppenheimer*[8] *(1914)*. The patient, a man aged 75 years, died suddenly after severe attacks of vertigo and tinnitus and of syncope, which he had had for over a year. The pulse rate was 20 to 36 per minute. Jugular and radial sphygmograms (published) showed complete heart block. The heart was not enlarged. There was severe coronary artery sclerosis. A large mass of calcium extended from the aortic leaflet of the mitral valve into the membranous portion of the interventricular septum. The aortic valve was thickened but not deformed. Careful histologic study showed that the calcium mass lay directly across the path of the bundle of His at its bifurcation and completely separated it from the origins of the bundle branches. Just before this point the bundle was fibrotic and contained small round cells. All small coronary arteries seen were considerably thickened.

5. *Monrad-Krohn*[9] *(1911)*. A woman, aged 75 years, had had attacks very suggestive of Adams-Stokes seizures for about a month. Until the last few days of life the pulse rate was usually about 60 per minute, but at times it would drop to 36. For about a week before death it apparently remained at this rate or lower (no tracings published). Death occurred in a convulsive seizure. The heart was somewhat enlarged. The mitral leaflets were infiltrated with calcium, and there were small deposits of calcium in the aortic valves. From the line of attachment of the aortic leaflet of the mitral valve a series of small masses of calcium spread out along the juncture of the membranous and muscular portions of the interventricular septum. Serial sections of this region showed the bundle of His compressed in its middle portion by masses of calcium above and below it. The bundle for some distance was very fibrotic and infiltrated with lymphocytes and plasma cells.

6. *Hoffmann*[10] *(1914) and Mönckeberg*[11] *(1916)*. A man, who had had Adams-Stokes attacks for five years, died at the age of 56 years. The ventricular rate had been 28 per minute except when he had tonsillitis, when it rose to 48. Polygrams and electrocardiograms (published) showed complete heart block with right bundle-

branch block.* The heart was moderately enlarged. There was sclerosis of the aorta, coronary arteries, aortic valve, mitral valve and pulmonary artery. A mass of calcium extended down from the base of the aortic valve into the membranous septum. Careful histologic examination showed the bundle of His completely destroyed by the calcium mass ("calcified thrombus") just before the point of division. The upper portions of both bundle branches were very fibrotic.

7. *Starling*[12] *(1921) and Lewis*[13] *(1922).* A man, aged 51 years, had had "fits" from November 1918 to May 31, 1919, during which time his pulse rate had been 60 to 80 per minute with normal a-c intervals except during the attacks. Swallowing sometimes caused the dropping of several ventricular beats but not after atropine was given. After May 31, 1919, there were no more "fits," and the pulse varied from 41 to 48 per minute with the auricular rate of 80 to 110 per minute as shown by polygrams (published). One day the patient dropped dead. Both ventricles were hypertrophied and dilated. The aortic valves were thickened at the edges by fibrous tissue and small masses of calcium. The anterior cusps were fused by calcification, and a mass of calcium extended from this point down into the left ventricle. The coronary arteries were dilated and atheromatous. Careful histologic study showed the A–V node to be normal. There was dense connective tissue about the first part of the bundle. The second half of the bundle was flattened, a little fibrous and contained small groups of lymphocytes. Near the bifurcation the bundle encountered the calcium mass in the septal muscle and was heavily damaged by fibrosis with lymphocytic infiltration. The upper part of both bundle branches was fibrous, as was the upper part of the septum.

8. *Yater and Willius*[2] *(1929).* A man, aged 74 years, had had Adams-Stokes attacks for three months. The ventricular rate was 40 per minute. Electrocardiograms (published) revealed multiple transitions which ranged from periods of normal sinus rhythm through varying grades of A–V block to remarkably long periods of asystole. Severe seizures of convulsive syncope became very frequent shortly before death, one lasting four minutes with complete cardiac standstill. The heart weighed 388 grams and showed moderate coronary artery sclerosis. There was a bar of calcium in the muscular portion of the interventricular septum below the juncture of the membranous and muscular portions most voluminous at the line of attachment of the aortic leaflet of the mitral valve. The bar of calcium lay beneath the bundle of His and greatly compressed the anterior half, which was invaded by fibrous tissue and some lymphocytes and plasma cells. The first portions of both bundle branches were fibrous, especially the right.

9. *Mahaim*[14] *(1931).* The patient was a man, aged 63 years, who had had dyspnea and syncopal attacks. The pulse rate was 36 per minute. Polygrams (published) showed complete heart block with auricular flutter or flutter-fibrillation and transitory bigeminy. There was a calcified nodule at the base of the aortic cusp of the mitral valve extending out into the membranous septum. Careful histologic examination showed multiple calcium masses in this region. The bundle of His was dislocated by the calcium and separated from the A–V node by a superior prolongation of the calcium mass noted grossly. The right bundle branch was separated from the main bundle and destroyed lower by fibrosis, while the anterior division of the left branch was destroyed by fibrocalcareous lesions. At the origin of these lesions there was stenosis of the right coronary artery. Small masses of calcium were disseminated through the upper part of the interventricular myocardium.

10. *Don, Grant and Camp*[15] *(1932).* A man, aged 68 years, had a pulse rate of 30 to 40 per minute, and electrocardiograms (published) showed complete A–V dissociation with great variation in the ventricular complexes from right to left bundle-branch block types, both abrupt and gradual. He died suddenly. The heart weighed 475 grams. Both ventricles were hypertrophied and dilated. There was

* The old terminology of bundle-branch block is used in this paper.

some coronary artery sclerosis without occlusion. A large nodule of calcium was located at the juncture of the aortic leaflet of the mitral valve with the interventricular septum and embedded in the myocardium of the septum. Careful histologic study showed the bundle of His to be destroyed by the calcium at its bifurcation and separated from the bundle branches.

These cases may now be compared with the one which we are reporting.

Case Report *

Clinical Case Record. The patient, a retired Army officer, aged 69 years, entered Walter Reed General Hospital, Washington, D. C., on January 15, 1933 and died January 21, 1933. His family history was irrelevant. Since 1914 he had been consistently treated for syphilis which had been acquired in 1902. He was known to have a fusiform aneurysm of the aorta, and his blood Wassermann reaction was always positive. Except for slight dyspnea on exertion, productive cough and occasional precordial discomfort, he felt quite well until December 24, 1932, which was four weeks before he died, when he began to have convulsive seizures, severe dyspnea, more intense precordial pain and swelling of the feet and ankles. His general strength failed rapidly, and he was confined to bed. Urination became burning and difficult, and the amount of urine small. He was emaciated and had a marked uremic odor of the breath. There were bruises over the entire body and bad ecchymoses

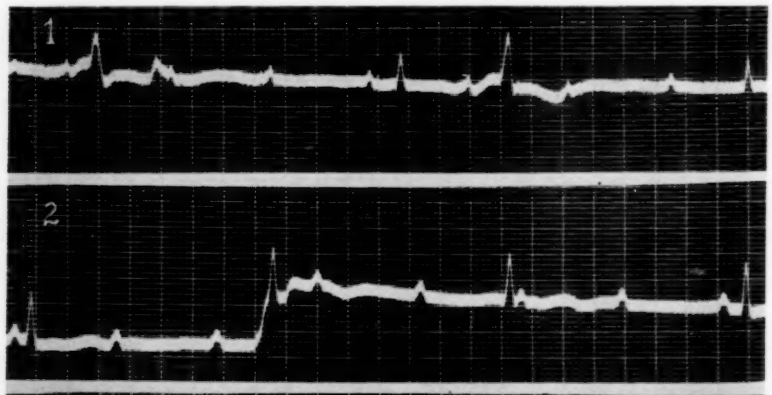

Fig. 1. Conventional leads of the electrocardiogram, showing complete auriculoventricular dissociation with premature contractions.

about the eyes and face. A bedsore was present at the end of the spine. The peripheral arteries were firm, beaded and tortuous. There was edema of the feet and ankles. The heart was slightly enlarged, and the ventricular rate was 40 to 45 per minute. A systolic and a diastolic murmur were present at the aortic area. There were moist râles at the bases of the lungs posteriorly. The abdomen was normal.

* Army Medical Museum Accession No. 40536.

The prostate gland was enlarged, "boggy" and tender. The hemoglobin was 80 per cent; the erythrocytes numbered 4,220,000 and the leukocytes 15,000 per cu. mm. of blood, with 83 per cent polymorphonuclear neutrophiles. The urine contained a few casts and a great deal of pus. The urea nitrogen was 40.5 mg. per 100 c.c. of blood. The blood Wassermann reaction was one plus, the Kahn reaction three plus. A roentgenogram of the chest showed a fusiform aneurysm of the arch of the aorta. An electrocardiogram showed the presence of complete heart block with auricular rate of 90 and ventricular rate of 50 per minute (figure 1). There were numerous premature ventricular beats from several foci. The T-wave was diphasic in Lead I and upright in Leads II and III. The congestion became progressively worse. On January 18 a severe convulsive seizure was followed by hemiplegia of the right side. On January 21 severe convulsive seizures occurred with violent movements of the left side of the body, the heart rate became slower and Cheyne-Stokes respiration ensued. Death occurred the same day in a convulsive attack.

*Necropsy.** Inasmuch as the main organ of interest to us was the heart, we shall merely note the anatomical diagnoses other than cardiac:

Arteriosclerosis, generalized, severe, with involvement of the cerebral and coronary arteries especially.
Pial edema and congestion.
Multiple areas of anemic softening of the cerebral cortex of the parietal and occipital lobes, left.
Syphilitic mesaortitis and aortic arteriosclerosis, with aneurysmal dilatation of the arch of the aorta, dilatation of the innominate artery and obliteration of the origin of the left carotid artery.
Moderate nephrosclerosis.
Prostatic hypertrophy, interstitial and adenomatous, with some urinary obstruction.
Dilatation, retention, trabeculation and small cellules of the urinary bladder, with chronic suppurative cystitis.
Senility, indicated by atrophy of the skin, etc.
Decubitus ulcer, sacral.
Subcutaneous edema, generalized, and especially of the right arm and leg.
Multiple abrasions of the body.
Pleural effusion, 800 c.c. left, 900 c.c. right, with depression of the diaphragm.
Partial atelectasis of the lungs.
Bronchopneumonia, acute, suppurative, terminal, bilateral, moderate.
Pulmonary edema and congestion, moderate.
Chronic passive congestion of the liver and spleen.
Emaciation and muscular atrophy.
Edentulous condition of the mouth.
Lymphadenitis chronic, tuberculous, inactive, of the peritracheal nodes.

Gross Description of the Heart. The heart weighed 430 grams, with moderate hypertrophy of the left ventricle. The pericardium and myocardium appeared normal. The endocardium and valves appeared normal except for the aortic and mitral valves. The aortic leaflet of the mitral valve was thickened, mainly by an elongated, calcified plaque, 2.5 cm. long, which extended out into the leaflet from its junction with the posterior cusp of the aortic valve. This plaque also extended far forward as an elongated pyramidal verrucous mass of calcium into the interventricular septum between the membranous and muscular portions, but it lay more in the muscular portion (figure 2). The greatest bulk of the mass of calcium was located at the line of attachment of the aortic cusp of the mitral valve, and just anterior to this it made a visible projection of about 0.7 cm. into the cavity of the left ventricle. The

* Performed by Major Hugh W. Mahon, M.C., U.S.A.

aortic valve presented calcification along the line of attachment to the aorta, and there was some fusion of the commissure between the anterior cusps and broadening and flattening of the commissure between the right anterior and the posterior cusps. The aortic sinuses were deepened and pouch-like. The orifices of the coronary arteries were surrounded by an atheromatous deposit but were not narrowed. The left coronary artery was thick-walled and tortuous, but its lumen was patent throughout. The right circumflex artery showed extensive atherosclerosis, with reduction of the lumen in its proximal third by about one half and in its middle third almost to obliteration, but beyond this its lumen was not so constricted.

FIG. 2. Roentgenogram of the opened heart after necropsy, showing the calcium mass in the interventricular septum.

Histopathologic Examination of the Heart. Two adjacent, large blocks of tissue were excised from the upper portion of the interventricular septum, which included most of the membranous portion and about the upper one-sixth of the muscular portion. These blocks included most of the calcium mass, the A–V node and bundle and the upper portions of the bundle branches. The blocks were called 1 and

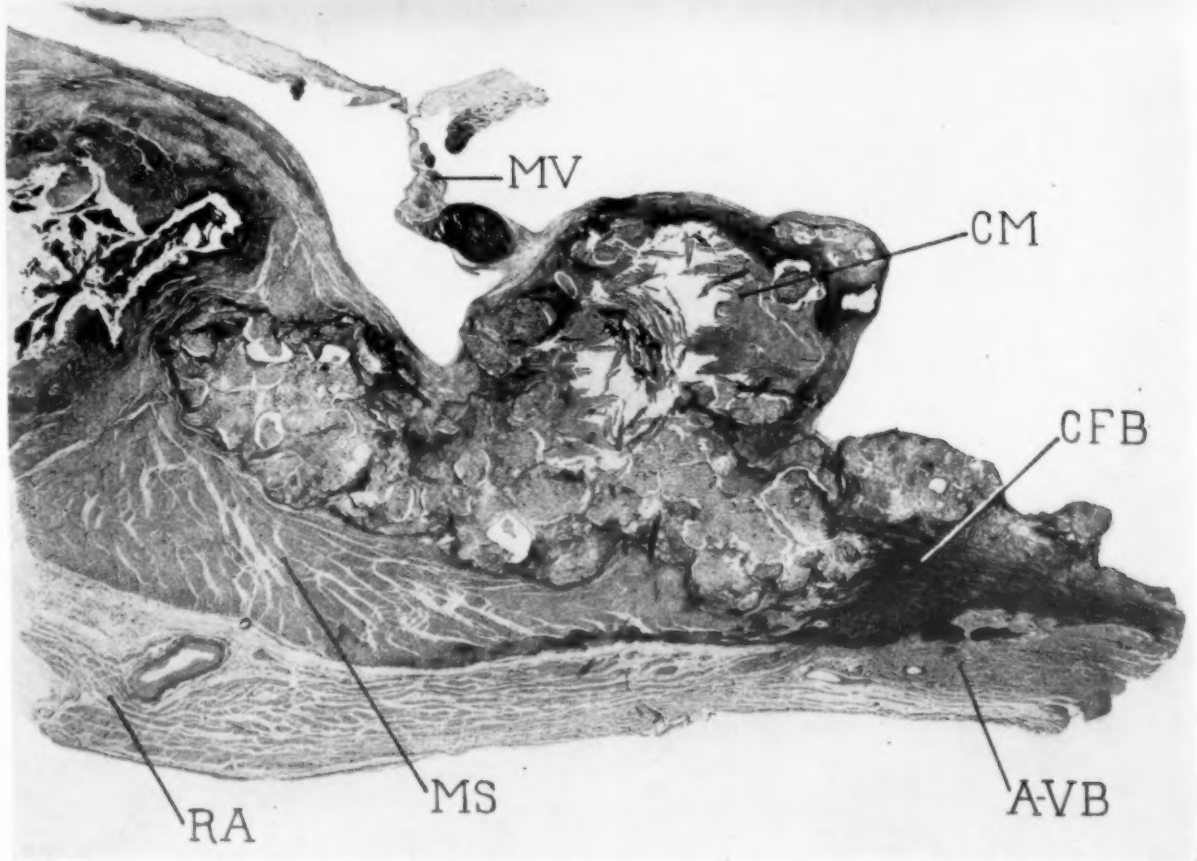

FIG. 3. Section 721 of block 1, showing the calcium mass, CM, in the interventricular septum, and the auriculoventricular bundle, A–VB, passing through the central fibrous body, CFB. MV, mitral valve; MS, muscular portion of the septum; RA, musculature of the right auricle. × 10.

2, block 1 being posterior to block 2. Serial sections 10 microns thick were made of both blocks after decalcification, and all were mounted and stained by van Gieson's method. Block 1 was cut horizontally from above downward and block 2 vertically from behind forward. Block 1 contained 945 sections; block 2 contained 677 sections. The upper edge of the calcium mass was observed first in section 365 of block 1. The mass became progressively larger and other masses appeared, which all fused into one large mass lower down. These masses were imbedded in the septal myocardium. They were homogeneous and yellowish, except one mass, which contained shattered black material. They were surrounded by a zone of fibrous tissue, which at some points contained groups of lymphocytes and plasma cells and at other points scattered lymphocytes. Occasional fibrous trabeculae traversed the masses. The upper edge of the A–V node was first recognized about section 550 of block 1. The entire node and about the first one-third of the bundle of His were contained in block 1. This portion of the conduction system was apparently normal (figure 3), except for moderate subintimal fibrosis of the artery of the node and a branch of this, which was completely occluded from its origin by endarteritis obliterans. This branch could be traced into the central fibrous body, where it skirted the edge of a nodule of calcium which projected slightly into the A–V node. The few other small arteries in the central fibrous body were also practically obliterated. The lower edge of the node was located about section 725 of block 1. The main mass of calcium was posterior and inferior to the A–V node and bundle and more on the left side of the septum. As the mass became smaller in the sections it was more continuous, elongated and of about the same thickness throughout, and it lay in the middle of the septal myocardium. The lower projections of the mass were seen to end in section 917 of block 1. The whole extent of the mass from above downward was, therefore, about 5520 microns or 5.5 mm. In block 2 the calcium mass and the bundle of His were present in the first section. The bundle was intact and normal, the calcium lying just below and slightly to the left of it (figure 4, I). Soon, however, the calcium mass spread out toward the right and adjoined the whole lower edge of the bundle. The calcium mass was similar to that in the lower part of block 1. One small artery below the mass was entirely occluded by an endarteritic process. Beginning about section 85 of block 2, a small mass of calcium was seen in the central portion of the bundle, with a little fibrous tissue surrounding it which contained a few lymphocytes (figure 4, II). This mass became rapidly larger, and by the time section 115 was reached it had come to replace about seven-eighths of the bundle, the remnant of which contained some fibrous tissue and lymphocytes (figure 4, III). The artery referred to above had continued in the septal musculature and developed a small lumen which gradually became larger. In section 140 there was practically no normal conduction tissue left in the bundle (figure 4, IV). The mass of calcium replacing the bundle and that originally below the bundle had become one mass. This condition existed until section 200, when some bundle tissue was seen on the right side of the calcium mass, and a small group of fibers was seen in the left lower portion which was the very first part of the left bundle branch (figure 4, V). The cross section of the calcium mass slowly became smaller, but for some distance the substance of the bundle was still more or less fibrotic, although the origin of the left bundle branch appeared to be quite normal (figure 4, VI). At the point of section 265 there was practically no calcium left, and beyond this the bundle and its left branch were quite normal (figure 4, VII, VIII). One small artery in the lower edge of the bundle had a thick wall. The bundle slowly continued on as the right bundle branch, the upper portion of which appeared to be quite normal (figure 4, IX). The whole extent of the invasion of the A–V bundle by the calcium was from section 85 to section 265 of block 2, a distance of 1800 microns or 1.8 mm. The diagram (figure 5) shows the general relationship of the calcium mass to the conduction system and the sites of the sections shown in figure 4. Inasmuch as the auriculoventricular dissociation had been thor-

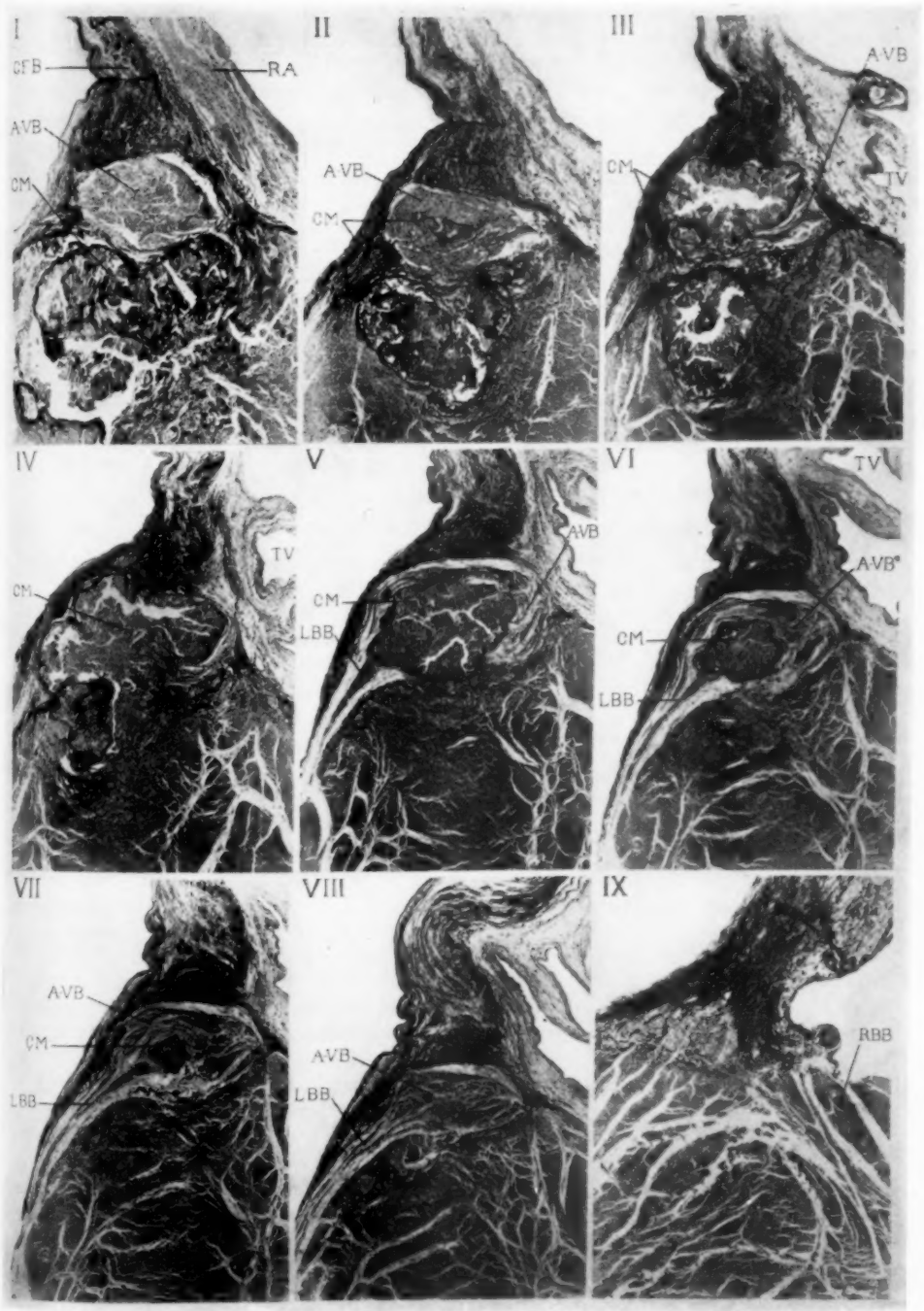

FIG. 4. Photomicrographs, numbered serially, showing the main portion of the conduction system at successive points in block 2. Compare with the text and the diagram, figure 5, for orientation. CFB, central fibrous body; RA, right auricle; A–VB, auriculoventricular bundle; CM, calcium mass; TV, tricuspid valve; LBB, left bundle branch, RBB, right bundle branch. Reduced from a magnification of 44 diameters.

oughly explained by the study of blocks 1 and 2 the bundle branches were not examined in the remainder of their course. The myocardium appeared to be quite normal, and the only intra-myocardial arteries altered to any extent that were observed were those already mentioned in the vicinity of the mass of calcium.

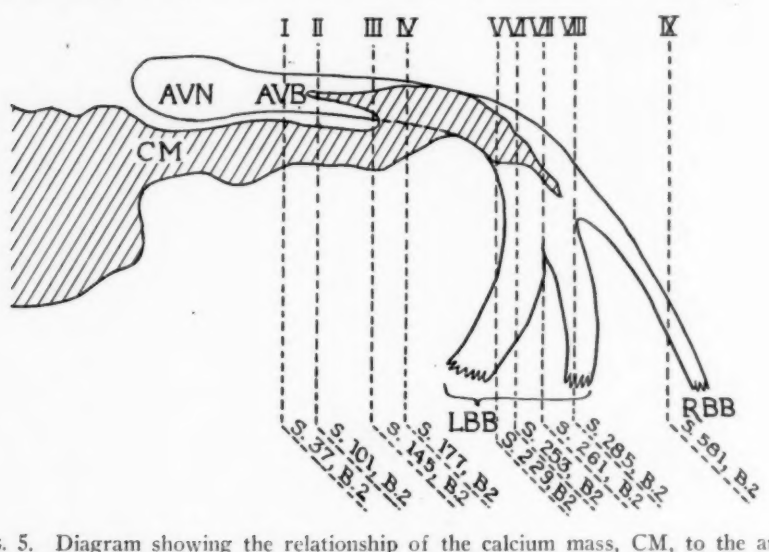

FIG. 5. Diagram showing the relationship of the calcium mass, CM, to the auriculoventricular node, AVN, the bundle of His, AVB, the left bundle branch, LBB, and the right bundle branch, RBB. The vertical interrupted lines show the planes of the sections reproduced in figure 4, with corresponding Roman numerals above and section and block numbers below.

Summary of Examination of the Heart. The heart was moderately enlarged. The pericardium and myocardium grossly were apparently normal. There was moderately severe sclerosis of the left coronary artery and almost complete occlusion by sclerosis of the circumflex branch of the right coronary artery. A large, verrucous mass of calcium was located at the base of the aortic leaflet of the mitral valve which extended out into this leaflet and also forward into the interventricular septum, mainly in the upper edge of the muscular portion. There was also calcification along the line of attachment of the aortic valve, with some fusion of the anterior cusps of this valve. Serial sections through the portion of the interventricular septum containing the main part of the conduction system showed the latter structure to be normal except in the middle third and part of the anterior third of the bundle of His, which was invaded for a distance of 1.8 mm. by the calcium mass lying mainly below it. At about the middle of this portion of the bundle the calcium had completely replaced it. The end and bifurcation of the bundle and the upper portions of the bundle branches were apparently normal. There was some fibrosis of the bundle with some lymphocytic infiltration surrounding the calcium mass. Some of the smaller arteries in the region of the calcium mass were very sclerotic and were occluded in places. The myocardium and the other intra-myocardial arteries were essentially normal.

DISCUSSION

The 10 cases of heart block which we have collected and abstracted from the literature and the one we have just reported show striking similarities. All of the patients were more than 50 years of age at the time of death.

Only two were in the sixth decade of life and five were in the eighth decade. Nine of the patients were males. Ten had had Adams-Stokes attacks, and most of them died in an attack. In one case the clinical history was not recorded. The accumulation of calcium in nine cases was present essentially and mainly in the same location, namely, at the base of the aortic leaflet of the mitral valve and extending out into the interventricular septum at the juncture of the membranous and muscular portions. In two cases it extended down into the septum mainly from the aortic valve. Either the auriculoventricular node or bundle was completely destroyed at one point or another by the invasion of calcium (in seven) or mainly by fibrosis due to compression by the calcium (in four).

The presence of coronary artery sclerosis was not so constant as the advanced age of the patients and the location of the calcium mass. It was present in at least seven cases, but it was of severe grade apparently in only three. The myocardium showed significant fibrosis in very few. From these facts it is impossible for us to believe that the calcific lesions were primarily due to vascular disease. It is true that in some cases the smaller coronary arteries in the region of the calcium mass were severely affected by sclerosis, but this could have been just as probably a change secondary to the deposition of calcium as preliminary to and causative of it.

The presence of calcium at the base of the aortic leaflet of the mitral valve is not uncommon in the hearts of older individuals, and extension of this lesion into the interventricular septum may occur without involvement of the conduction system, although the chance for such involvement when the calcareous lesion is extensive is great because of the location of the bundle of His.

It seems probable to us that the deposition of calcium in this region is usually due to stress and strain. The main mass of the heart is really hanging from the membranous portion of the interventricular septum, and the point of junction of this part of the septum with the muscular portion of the septum and the aortic leaflet of the mitral valve is undoubtedly one of great stress and strain, both during systole and diastole. As age advances and the vascularity of the heart is reduced by natural causes calcium becomes deposited at this point. In rare cases, as perhaps in those of Hoffmann and Mönckeberg and of Starling and Lewis, calcification of endocarditic thrombi of the aortic valve may be the manner of pathogenesis.

These cases, particularly that of Yater and Willius, indicate that the bundle of His may be seriously damaged and still function normally from time to time. Apparently only a few fibers are necessary for normal functioning. On the other hand, vagal action or toxic substances may so depress a partially damaged bundle as to prevent it from functioning.

It is interesting to note that although the conduction system apparently functions like nervous tissue it is anatomically muscular tissue. The auriculoventricular bundle may be completely destroyed in one portion and yet

be quite normal above and below this point, as is so well demonstrated by the case we have reported.

Summary and Conclusions

1. The acceptable cases reported in the literature of auriculoventricular heart block due to calcareous or fibrocalcareous lesions of the conduction system have been reviewed, and a new case has been reported.

2. The calcium mass in such cases usually extends from the base of the aortic leaflet of the mitral valve into the interventricular septum at the juncture of its membranous and muscular portions and invades the auriculoventricular node or bundle, which lies in this region.

3. The subjects of this disease are older individuals who do not necessarily have significant coronary artery sclerosis, and whose hearts usually do not show evidence of endocarditis.

4. The pathogenesis in most cases is probably the deposition of calcium at the point of greatest stress and strain in the heart; in other cases it may be due to calcification extending down into the membranous septum from old aortic endocarditis.

5. The conduction system above and below the point of destruction is frequently quite normal, thereby demonstrating the non-nervous structure of this system.

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QUANTITATIVE STUDIES ON INCREASED POTENCY OF LIVER EXTRACT BY INCUBATION WITH NORMAL HUMAN GASTRIC JUICE *

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THE therapeutic effectiveness of liver and fractions of liver in the treatment of pernicious anemia is well established. Minot, Cohn, Murphy, and Lawson [1] demonstrated that although slight reticulocyte responses followed the daily feeding of 60 grams of cooked liver, near-maximal responses did not usually occur unless from 150 to 200 grams of cooked liver were fed. Minot, Murphy, and Stetson [2] stated that: "There is apparently some minimal amount of liver in the vicinity of 60 gm. of cooked liver, which is a necessary daily amount to produce a distinct reticulocyte reaction when the red blood cells are about 1.25 million per cu. mm." Minot, Cohn, Murphy, and Lawson,[1] and Zerfas [3] have demonstrated that the amount of Liver Extract No. 343 derived from 300 grams of whole liver (from 12 to 14 grams of the dried powder) is about the minimal amount required to produce maximal reticulocyte reactions when fed daily to patients with pernicious anemia in relapse. Castle and his associates [4] later demonstrated that beef muscle, beef muscle protein, or yeast, after incubation with normal human gastric juice produced reticulocyte reactions when fed to patients having pernicious anemia, although the beef muscle, beef muscle proteins, yeast, and the gastric juice were ineffective when fed alone. Sharp,[5] Sturgis and Isaacs,[6] Conner,[7] Wilkinson,[8] and others have since shown that preparations of hog gastric tissue are likewise effective when fed daily in amounts equivalent to from 200 to 300 grams of fresh stomach tissue (from 30 to 40 grams of desiccated material). Following these studies Reimann and Fritsch [9] reported a thirty-fold increase in potency of whole liver by its digestion in normal human gastric juice. They reported that as small amounts as 10 grams of whole liver after incubation for two hours with 10 c.c. of human gastric juice produced near-maximal reticulocyte responses when fed daily to patients having pernicious anemia. Walden and Clowes [10] obtained an active preparation by the interaction of liver or liver extracts with small amounts of hog gastric tissues. Barnett and Thebaut,[11] however, were apparently unable to increase the activity of liver by its digestion with normal human gastric juice.

It is the purpose of this paper to report the results of the daily feeding to patients with pernicious anemia in relapse of varying subminimal amounts of Liver Extract No. 343 that had been incubated at 40° C. for from two to

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four hours with varying amounts of normal human gastric juice. These studies are part of a series attempting to determine the mechanism of the apparent increase in potency of liver and liver extracts, and to determine the relationship of the intrinsic factor of Castle, the active principle of liver, and extrinsic factors in the liver to this activation. Portions of these data have been presented elsewhere.[12, 13]

Methods

All of the test materials were administered daily by mouth for 10 days to patients having pernicious anemia in relapse. During the periods of study daily red blood cell counts, hemoglobin (Newcomer) determinations, and reticulocyte counts were made. The patients received meat-free, low vitamin B_2 diets during the test periods. The noon meal was given between 11 and 11:30 a.m. and the patients then received no food until 6:30 p.m. The liver extract-gastric juice digests were brought to pH 5.0 by the addition of sodium hydroxide immediately before the administration to the patients at 4:30 p.m. The patients having slight or no reticulocyte responses or clinical improvement responded to known potent materials administered by mouth before the experiments were considered negative.

Results

The responses of the red blood cells, hemoglobin, and reticulocytes to the various preparations are recorded in table 1. It can readily be seen that there was no response of the blood to the amount of liver extract derived from 100 grams of whole liver (4.5 grams of powder), to 150 c.c. of normal human gastric juice, or to 0.5 or 1.0 gram of liver extract which had been incubated with 100 c.c. of gastric juice. There was a very slight response of the reticulocytes (3.4 per cent at a red blood cell level of 1.37 million) but no clinical response when 2 grams of liver extract after incubation with 100 c.c. of gastric juice were fed to Case 5. There was a rise in reticulocytes up to 18.8 per cent (at a red blood cell level of 1.60 million) when Case 4 received daily 3 grams of liver extract which had been incubated with 100 c.c. of gastric juice. However, there was little rise in the red blood cells, and the clinical improvement was not marked. The administration of Extralin was followed by another reticulocyte rise up to 13.0 per cent (at a red blood cell level of 2.63 million) and a very satisfactory clinical improvement. An apparently maximal reticulocytosis (23.4 per cent at a 1.53 million red blood cell level) followed the administration of 4 grams of liver extract which had been incubated with 100 c.c. of gastric juice. A satisfactory clinical improvement followed this response, although a further rise in reticulocytes up to 6.2 per cent at a 3.14 million red blood cell level followed the subsequent administration of Extralin. There were maximal reticulocyte responses (24.4 and 21.2 per cent at red blood cell counts of 1.67 and 1.69 million, respectively) and satisfactory clinical improvement when 4.5 grams of liver extract (the amount derived from 100

grams of whole liver) were incubated with 100 c.c. of gastric juice and fed to Cases 1 and 2.

Slight but definite reticulocyte responses followed the administration of 4.5 grams of liver extract which had been incubated with 10 and 25 c.c. of gastric juice, while the response to 4.5 grams of liver extract incubated with 50 c.c. of gastric juice was very nearly maximal (17.2 per cent with a red blood cell count of 2.00 million).

TABLE I

The Responses of the Red Blood Cells, Hemoglobin (Newcomer), and Reticulocytes of Patients Having Pernicious Anemia to Various Test Materials and to a Known Potent Therapeutic Agent (Extralin)

Days	Case 1 — 4.5 gm. L. E.*			Case 2 — 150 c.c. G. J.†			Case 3 — 0.5 gm. L. E. + 100 c.c. G. J.		
	R. B. C. per cu. mm.	Hgb. %	Ret. %	R. B. C. per cu. mm.	Hgb. %	Ret. %	R. B. C. per cu. mm.	Hgb. %	Ret. %
0	1,750,000	39.5	0.3	1,440,000	33.0	0.7	2,870,000	70.2	2.1
1	1,640,000	37.3	0.4	—	—	1.0	2,680,000	68.8	1.2
2	1,310,000	34.4	0.1	1,310,000	31.8	0.3	2,680,000	59.8	2.2
3	1,300,000	—	1.0	1,550,000	34.4	0.4	—	—	1.7
4	1,570,000	37.0	0.1	1,300,000	43.0	0.6	—	—	2.1
5	1,310,000	33.0	0.4	1,370,000	35.8	0.4	2,650,000	63.7	2.4
6	1,220,000	30.7	0.8	1,270,000	30.7	0.5	2,730,000	64.0	1.7
7	1,480,000	31.9	0.8	1,350,000	34.4	0.4	2,460,000	57.0	1.4
8	1,360,000	31.5	0.7	—	—	1.1	2,380,000	56.4	1.1
9	1,210,000	30.3	0.9	1,390,000	32.7	1.1	—	56.4	1.2
10	—	—	0.9						
11									
12									
13									
14									
15									
16									
17									
18									
							Extralin, caps. 4 t.i.d.		
0							2,380,000	56.4	1.1
1							—	56.4	1.2
2							—	—	1.6
3							2,800,000	59.3	1.1
4							2,390,000	61.4	1.6
5							2,750,000	68.8	3.0
6							2,550,000	65.5	3.6
7							2,230,000	58.0	3.8
8							2,140,000	54.2	5.6
9							—	—	4.2
10							2,150,000	55.5	4.6

* Liver Extract No. 343.
† Gastric Juice.

Table 1 continued on next page.

TABLE I—*Continued*

Days	Case 4 1 gm. L. E. + 100 c.c. G. J.			Case 5 2 gm. L. E. + 100 c.c. G. J.			Case 4 3 gm. L. E. + 100 c.c. G. J.		
	R. B. C. per cu. mm.	Hgb. %	Ret. %	R. B. C. per cu. mm.	Hgb. %	Ret. %	R. B. C. per cu. mm.	Hgb. %	Ret. %
0	1,440,000	37.8	0.2	1,340,000	34.7	1.2	1,360,000	33.4	0.2
1	1,390,000	35.1	0.6	—	—	1.6	1,200,000	37.1	0.4
2	—	—	0.9	1,230,000	35.1	1.9	1,320,000	34.4	0.2
3	1,370,000	31.8	—	1,420,000	41.5	1.7	1,160,000	—	0.2
4	1,270,000	31.8	0.4	1,600,000	38.2	1.1	1,130,000	27.0	0.5
5	1,410,000	31.2	0.9	1,510,000	—	2.0	1,070,000	22.9	0.9
6	1,120,000	38.2	1.8	2,080,000	35.1	2.1	—	—	5.2
7	1,270,000	31.8	1.5	1,450,000	40.0	2.8	1,430,000	26.6	12.2
8	1,390,000	33.0	0.9	—	—	2.6	980,000	29.0	16.5
9	—	—	0.6	1,370,000	37.0	3.4	1,600,000	30.2	18.8
10				1,460,000	34.7	2.1	1,400,000	30.7	16.5
11							1,360,000	34.4	10.2
12							1,660,000	37.3	8.0
13							—	—	7.2
14							1,780,000	47.8	6.7
15									
16									
17									
18									
							Extralin, caps. 4 t.i.d.		
0							1,780,000	47.8	6.7
1							2,050,000	49.1	6.0
2							1,670,000	47.1	2.5
3							1,860,000	50.8	3.0
4							1,790,000	54.5	3.2
5							1,740,000	55.6	5.1
6							—	—	10.4
7							2,240,000	65.0	13.8
8							2,630,000	55.0	13.0
9							3,000,000	64.3	6.0
10							2,660,000	69.5	6.0

Table 1 continued on next page.

SUMMARY AND CONCLUSIONS

The incubation of Liver Extract No. 343 with normal human gastric juice markedly increases the potency of the liver extract. There is, however, a definite relationship between the amounts of liver extract and gastric juice necessary to produce maximal reticulocyte responses when the combination is fed daily by mouth to patients having pernicious anemia. It was found that near-maximal responses did not follow the administration of smaller amounts than 4 grams of liver extract (that derived from approximately 90 grams of whole liver) even after it had been incubated with 100 c.c. of gastric juice. The responses that occurred after the administration of smaller amounts were distinctly submaximal. To increase the potency

of 4.5 grams of liver extract satisfactorily 50 c.c. or more of gastric juice were required.

This increase in potency of liver extract is not nearly as great as that increase in potency of whole liver reported by Reimann and Fritsch when they incubated whole liver with human gastric juice. They were able to induce nearly maximal responses when they fed daily as little as 10 grams of whole liver which had been incubated with only 10 c.c. of gastric juice. Minot, Cohn, Murphy, and Lawson were unable to produce near-maximal reticulocyte responses unless the amount of cooked liver derived from approximately 200 to 250 grams of whole liver was fed daily to the patients, yet they stated that: "The administration daily of the amount of active principle extracted from 300 grams of liver is sufficient to produce a very

TABLE I—*Continued*

Days	Case 5 4 gm. L. E. + 100 c.c. G. J.			Case 1 4.5 gm. L. E. + 100 c.c. G. J.			Case 2 4.5 gm. L. E. + 100 c.c. G. J.		
	R. B. C. per cu. mm.	Hgb. %	Ret. %	R. B. C. per cu. mm.	Hgb. %	Ret. %	R. B. C. per cu. mm.	Hgb. %	Ret. %
0	1,460,000	34.7	2.1	—	—	0.9	1,240,000	36.2	1.0
1	1,460,000	43.0	2.6	—	—	1.2	1,160,000	35.4	1.1
2	1,390,000	42.5	1.6	1,250,000	28.5	1.7	1,250,000	36.2	0.6
3	1,270,000	35.1	2.2	1,230,000	—	2.2	1,450,000	27.2	1.0
4	1,270,000	36.6	3.0	1,350,000	33.4	2.2	1,330,000	32.7	0.9
5	—	—	14.3	1,240,000	29.1	3.2	—	—	4.9
6	1,150,000	39.1	20.3	1,440,000	30.5	11.2	1,760,000	36.2	14.3
7	1,540,000	41.5	23.0	—	—	20.5	1,690,000	39.1	21.2
8	1,530,000	50.6	23.4	1,670,000	—	24.4	1,800,000	41.0	12.8
9	1,840,000	41.5	17.0	1,650,000	41.0	17.5	2,240,000	39.1	9.2
10	2,090,000	50.0	8.2	1,670,000	35.1	11.7	2,000,000	41.9	6.8
11	2,550,000	54.5	—	1,800,000	36.7	9.8	2,150,000	—	4.3
12	—	—	—	2,190,000	36.1	5.9	—	—	5.7
13	2,060,000	50.6	10.0	2,170,000	43.0	9.2	2,710,000	42.0	7.5
14	2,450,000	48.4	7.0	2,390,000	44.6	5.6	2,600,000	53.5	4.9
15	—	—	—	2,730,000	50.0	4.4	2,520,000	52.1	2.7
16	2,190,000	55.5	3.5						
17									
18									
	Extralin, caps. 4 t.i.d.			Extralin, caps. 4 t.i.d.			Extralin, caps. 4 t.i.d		
0	2,190,000	55.5	3.5	2,490,000	52.1	2.5	2,950,000	66.1	0.8
1	2,200,000	57.3	1.9	2,800,000	47.8	—	2,790,000	55.5	0.3
2	2,120,000	53.0	1.4	3,020,000	47.8	0.2	3,270,000	55.5	0.9
3	—	—	2.0	—	47.6	—	3,320,000	63.7	0.8
4	2,300,000	55.5	0.4	2,430,000	44.1	1.1	3,150,000	58.3	—
5	2,370,000	56.4	1.2	2,730,000	50.6	—	3,110,000	56.4	1.3
6	2,440,000	59.3	4.2	2,980,000	52.9	2.1	3,450,000	65.5	0.9
7	2,260,000	54.5	3.8				3,060,000	65.5	0.2
8	2,600,000	60.2	6.0				3,630,000	67.5	0.4
9	3,140,000	67.4	6.2				3,520,000	66.1	0.1
10	—	—	5.1				3,960,000	84.0	—

Table 1 continued on next page.

TABLE I—*Continued*

Days	Case 6 4.5 gm. L. E. + 10 c.c. G. J.			Case 6 4.5 gm. L. E. + 25 c.c. G. J.			Case 7 4.5 gm. L. E. + 50 c.c. G. J.		
	R. B. C. per cu. mm.	Hgb. %	Ret. %	R. B. C. per cu. mm.	Hgb. %	Ret. %	R. B. C. per cu. mm.	Hgb. %	Ret. %
0	1,670,000	31.3	0.1	1,460,000	30.5	5.2	1,440,000	34.7	1.0
1	1,730,000	31.0	0.6	1,550,000	35.2	4.5	—	—	0.8
2	1,430,000	35.2	0.6	—	—	6.1	1,720,000	32.7	0.6
3	1,580,000	31.4	0.6	2,020,000	34.7	8.1	1,670,000	32.7	0.4
4	1,340,000	26.0	1.0	1,610,000	39.5	3.5	1,530,000	32.3	0.8
5	—	—	—	1,530,000	39.5	2.3	1,790,000	37.3	2.8
6	1,250,000	27.0	2.6	1,460,000	40.4	4.4	—	—	6.9
7	1,440,000	30.8	4.8	1,520,000	42.0	5.1	1,500,000	30.8	14.6
8	1,550,000	31.4	9.6	1,560,000	42.0	2.6	1,940,000	33.2	17.4
9	1,480,000	31.8	5.3	—	—	5.7	2,000,000	32.7	17.2
10	1,460,000	30.5	5.2	1,700,000	42.0	8.4	1,930,000	38.6	15.6
11							2,150,000	41.6	14.1
12							2,310,000	38.2	10.1
13							—	—	13.8
14							2,510,000	42.0	12.8
15							2,400,000	44.6	11.6
16							2,370,000	47.8	7.7
17							2,380,000	47.8	5.0
18							2,840,000	50.6	4.3
				Extralin, caps. 4 t.i.d.			Extralin, caps. 4 t.i.d.		
0				1,700,000	42.0	8.4	2,840,000	50.6	4.3
1				1,810,000	42.5	8.0	2,540,000	44.1	2.5
2				2,020,000	44.1	6.3	—	—	3.7
3				1,940,000	47.8	6.9	2,630,000	47.1	1.8
4				2,180,000	50.6	12.7	2,440,000	50.6	1.5
5				2,170,000	49.0	11.9	2,480,000	55.5	1.8
6				—	—	13.7	2,910,000	55.5	3.0
7				1,830,000	53.0	7.7	2,980,000	50.0	3.4
8				1,980,000	52.9	5.5			
9				2,250,000	58.3	7.6			
10									

satisfactory response." These facts and subsequent extensive clinical experience with liver extract demonstrate that a goodly portion of the active principle of the liver is contained in the liver extract. It can therefore be assumed that the great difference in the increase in potency of whole liver and liver extract is due to a loss of " an extrinsic factor " in the liver during the process of extraction rather than to a loss of the " active principle " of the liver. In addition it can be assumed that the increase in potency of liver or liver extract is the result of an effect of the type described by Castle and his associates when human gastric juice is allowed to act on beef muscle, beef muscle extracts, and yeast, rather than an actual increase in the active principle originally present in the liver.

The fact that as small an amount as 10 c.c. of normal human gastric juice will increase the potency of 4.5 grams of liver extract so that slight

reticulocyte responses result when the digest is fed daily to patients having pernicious anemia, must be considered when a quantitative estimation of the amount of intrinsic factor in an abnormal gastric juice is attempted, as by Hartfall and Witts,[14] Spies and Payne,[15] and Beebe and Wintrobe.[16] The use of liver extract (approximately 4.5 grams) would seem to be a better source of the extrinsic factor in such tests, as maximal responses can be expected when sufficient intrinsic factor is present in the gastric juice when liver extract is employed as the extrinsic factor, and this is not always the case when beef muscle or yeast is used.

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THE CORRELATION OF MINERAL METABOLISM AND THE VEGETATIVE NERVOUS SYSTEM IN THYROID DISEASE *

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FOR the past 50 years medicine has been so dominated by bacteriologic concepts of etiology, that we have become accustomed to look for *the* cause of a given disorder. However, in modern biochemical studies of metabolic diseases we have learned that there is frequently a correlation of various factors in a state of equilibrium. For some time iodine deficiency was stressed as a cause of goiter. During the past century there have been occasional references to the importance of calcium in the water supply as a cause of thyroid disease. Again other investigators have ascribed an important rôle to bacterial contamination of the water supply. However, thyroid disease may be considered the end result of a complex biologic equation which may include one or more factors such as diet, climate, geographic and geologic location, infection, hygienic conditions, emotion, temperature, sex and heredity. In any of these predisposing factors calcium and iodine exert an important influence. In fact, it is now believed that there is normally a state of equilibrium between calcium and iodine which regulates thyroid function (Thompson [1]). In the presence of dietary excess in calcium and deficiency in iodine the thyroid gland develops hyperplasia.[2] With a dietary excess in iodine, the administration of calcium promotes the storage of colloid in the thyroid gland, as I have demonstrated in a previous report.[3] This tends to explain the therapeutic properties of calcium in clinical hyperthyroidism.[4] There is a negative calcium balance in thyrotoxic conditions, as is shown by the increased excretion of calcium in the stool and urine, though the blood calcium is usually normal (Aub [5]). As concerns iodine there is usually a normal blood level of 0.008 to 0.018 mg. per cent.[6] In thyrotoxic conditions the gland becomes depleted of iodine and colloid, while the blood iodine is elevated.

The vegetative nervous system is intimately involved in any consideration of thyroid function. The gland is supplied by fibers from the sympathetic and vagus nerves which terminate in the capillaries and glandular epithelium. Pathologic changes such as shrinkage, vacuole formation, and thickening of the neurofibrillae have been recorded in the superior cervical and celiac ganglia in Basedow's disease (Müller [7]). Friedgood [8] has discussed the rôle of the sympathetic nervous system in the pathogenesis of exophthalmic goiter. He reports the finding of inflammation, infiltration, degeneration and fibrosis in the cervical sympathetic ganglia of patients suffering from exophthalmic goiter. Most of the clinical symptoms of thyro-

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From the John McCormick Institute for Infectious Diseases.

toxic conditions may be explained by the alterations in tone of the vegetative nervous system, particularly excessive function of the excitor elements and diminished function of inhibitory elements.

For the experimental study of thyroid function we may use histologic methods, which are practical because the specific secretion of the gland, thyroglobulin, is contained in the colloid which accumulates within the acini, and which is readily demonstrated by the usual staining methods. Concerning the microscopic appearance, A. Kocher [9] notes that goiter with much eosinophilic colloid contains much iodine. The most striking histologic difference between goiters containing much and those containing little iodine is the size of the gland follicles. In a thyroid gland containing a large amount of iodine we find large follicles in great quantity and only a few groups of small follicles, while in a goiter containing little iodine nearly all follicles are small. Such observations, as well as the condition of the follicular epithelium, blood vessels and stroma, aid in the interpretation of morphologic changes in the thyroid gland in terms of its functional activity, especially when the conditions are controlled experimentally. The present study is an attempt to correlate the dietary factors, calcium and iodine with hyperfunction of the vegetative nervous system in their effects on the thyroid gland.

Experiments

A series of 50 white rats (150–200 grams in weight) were studied under varying conditions of iodine and calcium intake as well as adrenalin stimulation. Of these, six died early in the course of the experiments, leaving 44 animals for final study. The rats were observed in four groups as follows: Group I, a series of seven normal rats kept for two months on an average laboratory diet (bread, green vegetables) and in one instance on an ideal diet of powdered milk, green vegetables and cod liver oil. This should give a reasonable control group of normal thyroids on average and optimum diet. Group II, a series of 14 rats on a diet of pearl barley and distilled water for a period of two months. This diet is practically iodine free. Studies carried out by Forbes and Beegle [11] have demonstrated that there is no iodine present in pearl barley. Group III, a series of 13 rats fed on the iodine deficient barley diet and also stimulated daily by subcutaneous injections of 2 minims of adrenalin (1–1000). Group IV, a series of 10 rats received the barley diet, 3 per cent calcium lactate in the drinking water, and daily injections of adrenalin. At the end of the period of experiment (two months) the rats were chloroformed, the thyroids and trachea immediately dissected out, and fixed in 10 per cent formalin. The tissues were embedded in celloidin; thick sections (10–15 microns) were cut, and stained with hematoxylin and eosin. Thick sections were purposely taken to get an accurate concept of the shape and size of the thyroid follicles. In order to render the results as objective as possible the diameters of the thyroid follicles were measured with an ocular micrometer. By this means 100 follicles

TABLE I

	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Rat 7	Rat 8	Rat 9	Rat 10	Rat 11	Rat 12	Rat 13	Rat 14	Average
GROUP I Normal controls Average diameter 100 follicles in microns	174	242	244	224	213	201	289								251 microns
Thyroid measurements (each lobe)	6x3x1	6x3x1	5x2.5x1	6x3x1	6x3x1	6x3x0.5	6x3x2								
GROUP II Barley and distilled H_2O diet Average diameter 100 follicles in microns	154	55	34	59	41	33	14	24	29	39	29	66	60	42	48 microns
Thyroid measurements (each lobe)	7x2x2	6x3x2	6x2x1	5x2x1	6x3x1	6x2x1	6x3x2	5x3x2	5x3x2	5x3x2	6x3x2	6x2x1	6x3x1	5x3x1	
GROUP III Same diet plus adrenalin stimulation; average diameter 100 follicles in microns	338	395	102	148	390	371	108	97*	136	94*	128	106	79*		187 microns
Thyroid measurements	5x2x0.5	5x2x0.5	5x4x1	6x3x1	6x3x0.5	5x2x0.5	5x2x0.5	R. 8x5x3 L. 8x4x2	6x3x1	R. 8x3x2.5 L. 7x3x7	6x3x0.5	5x4x1	R. 7x3.5x1 L. 7x3.5x1		
GROUP IV Barley plus 3% calcium lactate drinking water plus adrenalin stimulation. Average diameter 100 follicles in microns	233	238	225	234	212	195	208	207	249	212					221 microns
Thyroid measurements	6x3x3	6x4x2	6x2x1	7x3x2	6x2x2	6x2x2	6x3x2	6x3x2	7x3x2	7x3x2					

* Hyperplastic goiter.

were counted in each rat thyroid and the average measurement recorded for each. (See table 1.) This figure, which I call the follicular index, is an indication of the amount of colloid, and offers a simple method of estimating and comparing colloid content. It is particularly valuable in studying the thyroid gland of small animals such as rats and mice, where it is rather awkward to dissect out and weigh the entire gland. The gross measurements (length by width by thickness) were also recorded with each rat. Most of the lobes measured were symmetrical and one measurement is recorded in the table. Where there was a difference the measurements are given for both lobes.

Discussion of Results

As recorded in the table, the normal control rats in Group I had an average follicular diameter of 251 microns. Group II on iodine deficient diet showed a follicular diameter of 48 microns. (See figures 1 and 2.)

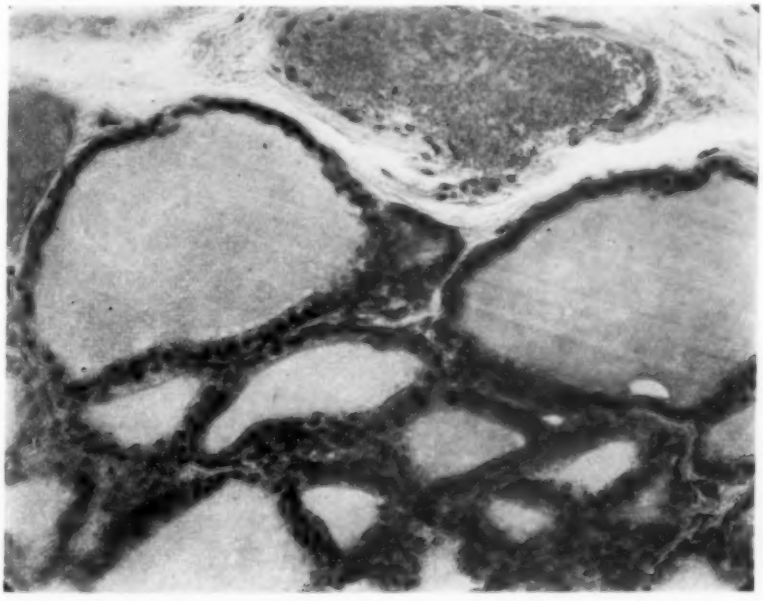

Fig. 1. Normal rat thyroid; optimum diet. High power.

This represents a loss of colloid down to 19 per cent of the normal amount. Microscopically the sections presented the solid appearance of a non-functioning fetal thyroid gland. The epithelium was cuboidal in character. There was also a definite capillary hyperemia. Group III, which had received an iodine deficient diet and daily stimulation with adrenalin showed an average follicular diameter of 187 microns. This indicates that adrenalin, even in the presence of iodine deficiency, stimulated secretion of colloid to such an extent that these glands retained 74 per cent of the normal amount of colloid. On gross examination this group showed three hyper-

plastic goiters with average lobe measurements of 8 by 5 by 3 as compared to the normal 6 by 2 by 1. Microscopically these sections were characterized by irregular contour of the follicles with a tendency to infolding of the epithelium, hyperplasia of the follicular epithelium, pycnosis and marked hyperemia. (See figure 3.) The areas of hyperplasia were suggestive of

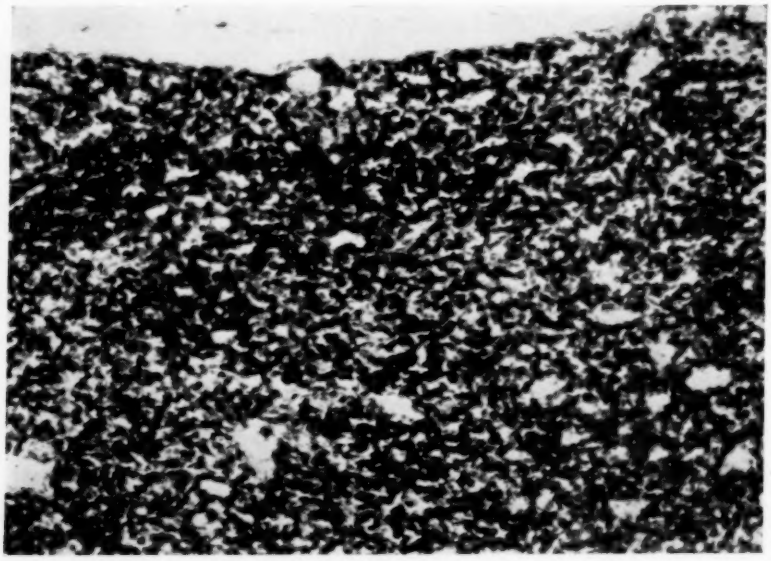

FIG. 2. Atrophic thyroid; iodine deficient diet. High power.

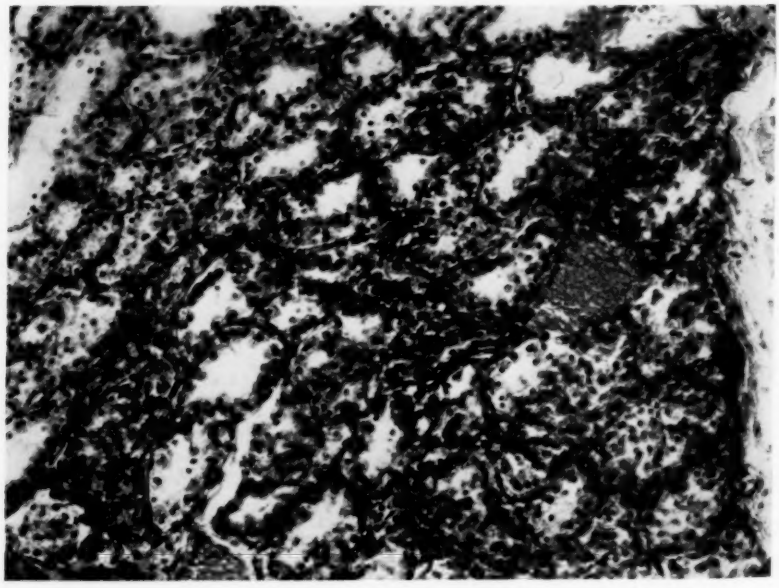

FIG. 3. Hyperplastic goiter: adrenalin stimulation: iodine deficiency.

the type seen in exophthalmic goiter. These rats also had varying degrees of exophthalmos as the result of sympathetic stimulation with adrenalin. Group IV, which received iodine deficient diet, adrenalin stimulation, and 3 per cent calcium lactate in the drinking water, showed the greatest amount of colloid storage with an average follicular diameter of 221 microns. This was 87 per cent of the normal value and demonstrated that in the presence of iodine deficiency and overstimulation of the sympathetic nervous system, calcium promotes the storage of colloid in the thyroid gland. Recent studies (Wahlberg [10]) indicate that the thyroid cell may secrete its colloid from either pole. Ordinarily the apical portion of the cell secretes the colloid vacuoles which are stored in the follicles. A small amount is secreted by the basal part of the thyroid cell directly into the blood capillaries. In colloid goiter the apical direction of secretion is pathologically increased, but qualitatively similar to the process in normal glands. In thyrotoxicosis the basal secretion mechanism predominates. The clinical improvement after preoperative iodine therapy in thyrotoxicosis corresponds to the reversal of polarity in secretion from basal to apical type with resultant storage of colloid in the follicles. In terms of these recent concepts it seems that in Group IV, calcium administration favored apical secretion in the thyroid epithelium and follicular storage of colloid. Microscopically these sections

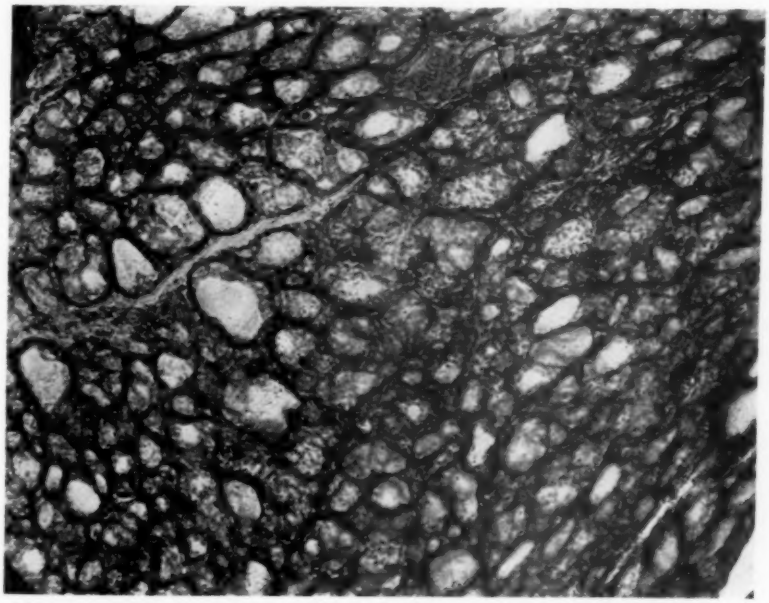

FIG. 4. Almost normal storage of colloid. Iodine deficient diet plus 3 per cent calcium lactate plus adrenalin stimulation.

looked normal (see figure 4). There was no hyperplasia and no hyperemia. The follicles were distended and the epithelium flattened by the stored eosinophilic colloid. There was a normal stroma. Ordinarily, excessive calcium ingestion associated with an iodine deficient diet causes hyperplastic changes.

However, in the presence of adrenalin stimulation there is a storage of colloid approximating normal conditions. This is further proof of the logical indication for calcium in the treatment of clinical hyperthyroidism.[4]

In summarizing the results it may be emphasized that iodine deficient diet caused atrophy of the thyroid gland. This finding confirms the work of Hellwig who concluded that dietary deficiency in iodine is not the essential cause of goiter. Furthermore, it was found that stimulation of the sympathetic nervous system in association with dietary deficiency in iodine induced marked hyperplasia, and in three out of a series of 13 rats, a definite hyperplastic goiter. Finally it was definitely demonstrated that calcium administration promotes the storage of colloid even under such unfavorable conditions as iodine deficiency and overactivity of the sympathetic nervous system induced by adrenalin stimulation.

Conclusions

1. A new method for estimating and comparing storage of thyroid colloid is described. The follicular diameter is measured by means of an ocular micrometer and the average taken of a large number of measurements.

2. Dietary deficiency in iodine causes atrophy of the thyroid follicles and loss of colloid.

3. Sympathetic stimulation with adrenalin in the presence of iodine deficiency causes hyperactivity of the thyroid epithelium with increased secretion of colloid, hyperplasia, hyperemia, and hyperplastic changes.

4. Calcium administration promotes colloid storage and neutralizes the harmful effects of sympathetic stimulation.

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DISEASES OF THE NERVOUS SYSTEM PRODUCING DYSFUNCTION OF OTHER ORGANS AND DYSFUNCTION OF OTHER ORGANS PRODUCING OR SIMULATING DISEASES OF THE NERVOUS SYSTEM *

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Dysfunction of respiration, circulation, secretion, excretion, digestion, growth, metabolism and reproduction occurs alike in diseases of the nervous system and of other organs. The signs and symptoms of such dysfunction necessitate the differentiation of such diseases.

The disturbances of function following encephalitis lethargica illustrate how diversified the dysfunction of the body may become as the result of a disease of the nervous system. To note a few of these disturbances, mention may be made of the disorders of sleep, of somnolence, insomnia and reversal of time of sleeping, of the disturbance in temperature regulation, of hypothermia, associated with general lowering of metabolism, slow pulse and respiration and low blood pressure, of respiratory dysfunction, yawning, inspiratory and expiratory spasm, marked hyperpnea so severe as to produce tetany, of changes in sweating, hyperhidrosis, seborrhea, of secretory disturbances, sialorrhea and lachrymation, polydipsia, polyuria, at times changes in sugar and fat metabolism, glycosuria and adiposity, of menstrual disturbances, amenorrhea, and myasthenia which may be indistinguishable from that of myasthenia gravis.

Functional nervous disease as is found in the neuroses may produce dysfunction of all of the organic functions. Some may be enumerated, although they need not be discussed at this time. The functional manifestations of the digestive system include anorexia, excessive and perverted appetite, dyspepsia, vomiting, dilatation of the stomach, diarrhea, constipation, spasm of the intestines and mucous colitis. Dysfunction of the urinary organs may appear as frequency of micturition, interrupted micturition, painful micturition, polyuria, ischuria and relative anuria, incontinence and rarely retention of urine. The genital troubles of man include spermatorrhea, impotence, absence of ejaculation, premature ejaculation, painful ejaculation and loss of sensations. In women, frigidity, spasms, contractures, pains and amenorrhea. Nasal and laryngeal troubles, spasm of the vocal cords, aphonias, respiratory difficulty, air hunger, and pseudo-asthma occur. Symptoms related to the cardiovascular system are very common such as palpitation, pains, feelings of oppression and the numerous phobias attached to these. Pallor, vasodilatation, disturbances of sweating, cutaneous disturbances, all may be mentioned. In the neuromuscular apparatus, fatigue, weakness, disturbance of equilibrium, tremors and other hyper-

* Read at the Chicago meeting of the American College of Physicians, April 20, 1934.

kinesias occur, as well as contractures and "paralysis." Hyperesthesias, paresthesias and anesthesias occur, and manifold manifestations of the sense organs may be found. Disturbances of sleep are common, as are headache, speech disturbance and psychic change.

Organic disease of the nervous system likewise produces change in function of many organs. Disorders of the special senses may occur alike in disease of the nervous system and local disease.

When loss of smell occurs thought should be given to the possibility of lesions in the anterior cerebral fossa, as olfactory groove meningioma or tumor about the sella. Such olfactory disturbances are also often observed following basilar skull fracture. Sensations of unpleasant odors and other olfactory or gustatory hallucinations may be the result of lesions in the temporal lobe and occasionally may be misinterpreted as being the result of hysteria or another neurosis or psychosis. Defects in vision are of greatest importance in indicating disease of the nervous system and everyone should be familiar with the use of the ophthalmoscope and be able to determine for himself the presence of optic neuritis, optic atrophy and choked disc. Very frequently when vision is becoming defective, early recognition of a visual field defect may lead to an early diagnosis of a pituitary adenoma or a brain tumor. Sudden blindness, at times in one eye, without evidence of disease in the media or retina, may be the result of a retrobulbar neuritis in multiple sclerosis. Scintillating scotomata are the usual precursors of a migraine headache and may constitute the aura of a convulsion resulting from disease of the temporal or occipital lobe. Deafness, especially unilateral, of gradual onset associated with tinnitus and vertigo should call attention to the possibility of an acoustic neuroma or cerebellopontine angle tumor. Of course what the patient calls dizziness often is not a vertigo but a peculiar sensation of floating or sinking, unsteadiness, or blurring of vision and need not be related to the eighth nerve.

Weakness in mastication may be the earliest sign of myasthenia gravis, or difficulty in chewing may be the result of defective movement of the tongue and be an early sign of disease of the medulla, bulbar palsy, amyotrophic lateral sclerosis or syringomyelia. It may also occur in the myopathies and progressive muscular atrophy. Defective swallowing may be the result of disease of the medulla or of myasthenia gravis, and often it is the consequence of postdiphtheritic paralysis; occasionally it occurs in other polyneuritides, or in pseudobulbar palsy which may be the result of bilateral, at times trivial, strokes, or of polioencephalitis. Pain produced by swallowing, often described by the patient as difficulty in swallowing, should call attention to the possibility of glossopharyngeal or trifacial neuralgia, or rarely, of multiple sclerosis or syringomyelia. Hydrophobia and spasms of the muscles of deglutition of course occur in rabies, and trismus is commonly seen in tetanus. Peculiar tic-like movements of the jaws and tongue are seen in the dystonias following encephalitis lethargica. Attacks of smacking

the lips are manifestations of epilepsy and are associated with some modifications of consciousness.

Dysarthria, frequently attributed to faulty fitting dentures or edentation, should call attention to the possibility of paresis, multiple sclerosis, disease of the medulla, Friedreich's ataxia; it also occurs, of course, in vascular accidents of the brain. Defects in phonation, with paresis of the vocal cords, are seen in tabes dorsalis and in disease of the medulla. When associated with dysphagia and nasal speech they may be a part of the picture of involvement of the vagospinal nerves from metastatic growths, or due to a lesion of the pons resulting from thrombosis of the posterior-inferior cerebellar artery. Spasm of the glottis in children results from tetany, and in adults is due most commonly to the laryngeal crisis of tabes but is seen also in rabies and in tetanus. Stertorous respiration, Cheyne-Stokes' respiration, Biot's respiration are found in the comas due to disease of the nervous system such as the apoplexies, brain tumor, abscess, meningitis; and likewise appear in general disease such as uremia, diabetic coma, the toxemias of pregnancy, etc. Dyspnea occurs in labio-glosso-laryngeal paralysis; in bulbar palsies, including the bulbar type of anterior poliomyelitis; in polyneuritis; in myasthenia gravis and in the myopathies; in paralysis of the phrenic nerves as in cord tumor or myelitis; and in paralysis of the intercostal nerves in similar disease and in anterior poliomyelitis.

Attacks of hyperpnea, frequently associated with dystonic movements and trance-like states, occur as the result of encephalitis lethargica; and respiratory spasms occur in that disease and in tabes. Slow respiration occurs at times as an evidence of increased intracranial pressure and in the state of hibernation produced by tumors of the pituitary gland. Hiccough is seen in bulbar disease, at times in anterior poliomyelitis, in myelitis, and particularly in some forms of epidemic encephalitis.

Among the disturbances of the function of the heart, palpitation may be observed in disease of the medulla and in epilepsy. Symptomatic tachycardia may be seen in lesions of the pneumogastric nerve in mediastinal disease; in diseases of the structures of the neck, such as abscess or tumor; in tabes; and in alcoholic and diphtheritic polyneuritis. In labio-glosso-laryngeal paralysis, acute bulbar palsy, Landry's paralysis, acute anterior poliomyelitis and amyotrophic lateral sclerosis tachycardia is often observed. Bradycardia is characteristic of conditions producing increased intracranial pressure such as meningitis. It is seen occasionally in dementia paralytica, in multiple sclerosis and in melancholia. At times it is associated with the state of hibernation due to pituitary disease. Increase of general blood pressure may be seen as a consequence of increased intracranial pressure following trauma, and in tumors, and may also be found in cases of pituitary basophilism; while a low blood pressure may at times be seen in epilepsy and pituitary hibernation. Among the vascular signs, cutaneous hemorrhage occurs in anterior poliomyelitis, in meningitis, and at times in myelitis, in multiple sclerosis and in purpuric myelitis. Alternating pallor and flushing

are often seen in meningitis and especially in the tuberculous form of this disease. Vasomotor disturbances are frequently observed in bulbar lesions, with or without hemianesthesia. Dermographism is common in the meningitides, and in Quincke's edema. In the peripheral neuritides erythematous and exfoliative dermatitis may be observed. Raynaud's disease may be mentioned as producing local asphyxia and gangrene, and intense rubor of the skin is observed in erythromelalgia. Severe trophic disturbances, with gangrene and atrophy, are seen in syringomyelia, in disease of the cauda equina and in spina bifida occulta. Edema is often seen in cerebral lesions, usually when there is an associated cardiac failure and it occurs in the hemiplegic side. It is also seen in transverse lesions of the spinal cord, in tabes, in syringomyelia, in paralysis agitans and in multiple neuritis. Other metabolic disturbances of the skin are the localized painful accumulations of fat in adiposis dolorosa, and the adiposity and purplish striations in pituitary basophilism. Chronic cyanosis is often seen in catatonic dementia precox. Peripheral nerve lesions may result in cyanosis, erythema, glossy skin, keratosis, ulcerations and hypotrichosis. In lesions of the cerebrum and even more in those of the spinal cord decubitus ulcers and mal perforans are found. Anhidrosis is found in transverse lesions of the spinal cord, in paralysis of the cervical sympathetic and locally in lesions of the trigeminal nerve.

Many of the acute infections of the nervous system, such as meningitis, encephalitis and anterior poliomyelitis, are associated with constipation or at other times with diarrhea. Vomiting unassociated with the time of eating and often without nausea, projectile in character, sudden in onset, and at times occurring with headache and vertigo are characteristic of intracranial hypertension in tumors. At times what has been considered cyclic vomiting and acidosis of childhood has been found to be the result of a midline cerebellar tumor, producing few other localizing signs. Vomiting frequently occurs in lesions of the cervical spinal cord, occasionally in myelitis and often in the form of crises in tabes. In tabes also enteric crises with pain and constipation occur. Diarrhea is sometimes observed in tabes, although constipation, at times with tenesmus, is the rule. In transverse lesions of the cord constipation is found and in tabes and lesions of the conus and cauda equina incontinence is frequent.

Glycosuria may be found in lesions of the upper cervical cord, and albuminuria in cerebral hemorrhage, in brain tumors and in meningeal hemorrhage. The renal crises of tabes simulate renal colic.

Derangement of the bladder function may be brought about from a lesion of any level of the spinal cord and from disease of the cauda equina. Among the diseases giving rise to such derangements mention may be made of the following: transverse lesions of the spinal cord due to myelitis or caused by compression from diseased vertebrae, or from tumors, etc., diffuse diseases, as multiple sclerosis, disease of the posterior roots and columns, as in tabes

dorsalis, syringomyelia, tumors of the cauda equina, root neuritis and spina bifida occulta.

When the defects of function of the nervous system are pronounced the cause of a disturbance of bladder function may be apparent, but it not infrequently occurs that the earliest sign of some of these diseases is related to the function of the bladder. In diseases producing a transverse lesion above the level of the reflex arc of the bladder sphincter, difficulty in starting the urinary stream is noted and at times dribbling may appear. The function of the bladder is interfered with in almost every case of tabes dorsalis. At times in addition to difficulty in starting the stream there is a lessened desire to micturate for long periods of time. Incontinence is frequently observed, early in the disease limited to a small amount sometimes after voluntary urination. Attention should be drawn to the occurrence of crises in tabes. Clitoridean crises in the form of paroxysms of voluptuous sensations with vulvovaginal secretion have been noted. Renal crises with severe pain in the region of the bladder and kidneys, eventually accompanied by dysuria, may appear. At times lightning pains may have their seat in the bladder and perineum. Disagreeable sensations during urination, and frequent and imperative desire to urinate are often observed. Difficulty in completely emptying the bladder with retention of residual urine is common.

In general, multiple neuritis is not associated with bladder disturbances but in a number of instances such disturbances have been known to occur. Bladder disturbances are not characteristic of amyotrophic lateral sclerosis, the spinal atrophies or myopathies.

Lesions of the cauda equina and spina bifida occulta may result in either retention or incontinence of urine.

Disturbances of menstruation, irregularity, infrequency and cessation are often among the first signs of disease of the pituitary gland and its environs, occurring with sufficient frequency to merit careful consideration.

In disease of the spinal cord sexual impotence frequently occurs. It is often seen in tabes dorsalis, in transverse lesions of the cord, in multiple sclerosis, and in lesions of the conus and cauda equina. Changes in the joints of the type known as Charcot joints may be seen in tabes and syringomyelia; other arthropathies are found in hemiplegia and peripheral nerve lesions. Atrophy of bones occurs in peripheral nerve lesions, in anterior poliomyelitis, in the myopathies, syringomyelia, tabes and dementia paralytica. In the last named three diseases spontaneous fractures are common. Arrested development of bone follows the cerebral palsies and the spinal paralyses of childhood.

Among the diseases producing disorders of the nervous system infectious diseases are paramount. In children encephalitis, leading to mental deficiency, cerebral palsies and epilepsy, is not an uncommon complication of the exanthemata as measles and scarlet fever, and of whooping cough. Meningitis likewise occurs, more frequently as the result of tuberculosis, pneumonia and influenza, but occurs in other infections as well. Venous

sinus thrombosis of the pyogenic variety often results from general septicemia, especially of the puerperal variety; and as the result of adjacent inflammatory lesions in the sinuses and mastoids. In similar conditions brain abscess and meningitis may occur. Non-pyogenic venous sinus thrombosis occurs in cases of cachexia in nutritional disorders or other wasting diseases. Hemiplegia due to cerebral arterial hemorrhage, thrombosis or embolism is dependent upon underlying disease for its cause. Cardiovascular renal disease with hypertension frequently occasions cerebral hemorrhage; syphilitic arterial disease in the brain often leads to thrombosis; in active endocarditis and in bronchiectasis with local thrombophlebitis emboli are readily detached which may lodge in the brain. Diseases of the blood, as polycythemia, are often the causes of cerebral hemorrhage, and of thrombosis of cerebral vessels. Chorea is usually due to the rheumatic infection with accompanying endocarditis. Another type of chorea may be associated with pregnancy.

Degeneration of the spinal cord, as in combined degeneration of the spinal cord, is most frequently associated with pernicious anemia. Often the blood picture shows only a macrocytosis without anemia, but an achlorhydria is constant. Dietary deficiency diseases, such as pellagra, likewise produce degeneration of the spinal cord; and lesions in the spinal cord and peripheral nerves are seen in diabetes. In leukemia, infiltrations of the cord and brain occur, and of course metastases in these tissues may arise from any malignant tumor. The peripheral nerves are often affected by a multiple neuritis in diphtheria—less frequently in other infectious diseases. Multiple neuritis is characteristic of one form of beri-beri, and occurs also in other deficiency diseases and in diabetes. Women in the puerperal period are peculiarly susceptible to its occurrence.

The importance of recognizing cerebral involvement in infectious diseases is emphasized by the frequency of cerebral edema and meningismus in all severe infections. Acute confusional and stuporous states are common. Delirium frequently occurs and evanescent hemiplegias and visual disturbances are frequently observed in uremia and eclamptic conditions. Often the underlying pathology of a state of delirium or confusion is unrecognized.

Of the greatest practical importance is the recognition and correct interpretation of those signs and symptoms which may occur alike in diseases which are primary in the nervous system and in those which are primary in other bodily structures.

Coma occurs often as the result of certain bodily diseases, such as uremia, eclampsia, diabetes and terminal states, and likewise in cerebral diseases, such as meningitis, encephalitis, hemorrhage, thrombosis, embolism, abscess, sinus thrombosis, and brain tumor. I would direct your attention to only one feature in the differential diagnosis, namely, hemiplegia. Although it is true that hemiplegia may occasionally be present in eclampsia and uremia, usually a hemiplegia calls attention to the existence of other brain lesions.

The coma may be so deep, however, that the hemiplegia may easily be unrecognized, unless carefully sought for. Usually the coma is not so deep but that pricking the face with a pin will produce some grimacing, and then, the one side will be seen to contract more efficaciously than the other. If the lids are open they are further open on the paretic side. The nasolabial fold is more shallow, and at times puffing of the paretic cheek is seen in expiration. When the arm is passively lifted, the forearm extended and so placed that when it is allowed to fall, it would fall upon the face, unless the coma is unusually deep the forearm is stopped in its fall by a voluntary contraction. It usually falls more slowly, and at times may be held extended. If paralyzed, it falls quickly without interruption. When the lower extremity is passively flexed at the knee and hip and released on the paralyzed side, it falls into external rotation and slides into extension. On the normal side it is often held in the midline for a time or slowly extended. When the foot is passively dorsal flexed, on the normal side a contraction occurs in the tibialis anticus. Even in the comatose state the deep reflexes may be increased on the paralyzed side, great care being exercised to compare the responses of the two sides, and often the abdominal, cremasteric and plantar reflexes are absent on that side. When the abdominal wall or chest wall is pricked with a pin the patient, if able, will reach toward the spot only with the normal hand. It is very important to remember that when the soles are pricked, movement of the leg does *not* mean that paralysis is not present, as this often is a reflex and frequently leads to a wrong diagnosis.

Convulsions occur in idiopathic epilepsy, in gross disease of the brain and as the result of intoxication in metabolic, toxic and infectious diseases. Very careful inquiry into the history is essential in making a differential diagnosis. Often it will be found that preceding attacks occurred, even years ago. Of particular importance are the occurrences of little attacks. Often these are of such short duration and mildness that their significance as petit mal attacks is overlooked. They may consist of flashes of apprehension, tightness in the throat, a lump in the throat, a gone feeling, a dizziness, a sense of dreaming, a hesitation in speech or a momentary cessation of activity. Often they produce so little disturbance that the patient attributes but little importance to them. At times they occur more frequently, just before or at meal time. Fortunately, most of them are of longer duration and are associated with changes in color, slight salivation, widening of the eyes and staring, so that others note the attacks.

Rarely one observes attacks of sudden, lightning-like movements of the shoulders and arms, as if shrugging and flinging the arms upward. This is an epilepsy. Occasionally terror-like attacks occur, in which the child may run to the mother, cling to her a few moments and then shamefacedly resume play.

Frequent stumbling without reason often calls attention to an epilepsy and in one form (cataplexy) a sudden loss of all muscular tone occurs with

the patient dropping down, and then immediately arising. Usually the attack is brought on by an emotion of risibility, surprise or pleasure. It is important to observe, however, that not all muscular twitching and tremors are convulsions. Hyperinsulinism with convulsions should not be treated as epilepsy.

Pain is one of the commonest symptoms of all disease. Headache, often a prominent symptom of intracranial disease, must be carefully studied, as it is often present in other disease and in functional states, as the neuroses. In the latter it is never a pain. Although it is described as excruciating, terrible and unbearable, it is always a sensation and never a pain. It is a tightness, a fullness, a throbbing, a trickling, a pressure, a bursting feeling. It is always made worse by mental effort and emotional disturbance. On the other hand, the pain of intracranial disease is a real pain. In brain tumor it is very severe, throbbing, bursting, and occurs often in attacks associated with vomiting. It is worse on coughing, sneezing and straining. Frequently it may be brought on and at times stopped by change of position of the head. In cerebellar disease it is frequently suboccipital and associated with a rigid neck. It occurs at any time of the day and, unlike the pain of sinus disease, is not affected by weather. Neither, as occurs in indurative headache, is there tenderness of the scalp, except in subtentorial lesions. Pains in the extremities and trunk are often attributed to a so-called neuritis or neuralgia. Unless there is evidence of diminished function of the nerve supposed to be involved, as paresis, loss of sensation, or change of irritability to electrical stimuli, the condition is not a neuritis but a referred pain. In the upper extremity the pain may be attributable to an arthritis of the shoulder or of the cervical spine or to a subacromial bursitis or a cervical rib. In the lower extremities it is usually the result of an osteo-arthritis of the spine, or of sacro-iliac disease, hip joint disease, or disease in the pelvis. Here it may more frequently be found that the sciatic nerve is actually secondarily involved in the lesion as shown by absent Achilles jerks.

To bilateral sciatica special attention must be paid, as it is not infrequently the sign of a lesion of the cauda equina. The Achilles jerks will usually be absent and anesthesia be found over the buttocks and sacral region, and the spinal fluid is often yellow or rich in albumin and globulin. The pains are radiating, burning, excruciating and always worse at night.

What is true of neuritis is even more true of neuralgia. With the exception of glossopharyngeal and trifacial neuralgia, the other algias are always referred pains from underlying pathologic lesions. In contrast to the face pains called neuralgic due to such diseases as sinus infections, infections about the teeth, etc., the pain of trifacial neuralgia occurs in attacks of very short duration and is provoked by stimulating a "trigger zone," by touch, chewing, talking and swallowing.

Root pains due to spinal cord tumors, tabes dorsalis, or pachymeningitis, when they occur in areas usually the site of pain in biliary, renal and

appendiceal disease, should not lead to useless abdominal operations; and the pains produced by disease of the spine, by osteo-arthritis, osteomalacia and tuberculosis should not be interpreted as being produced by spinal cord lesions. In the former instance careful examination will elicit defects in motion, sensation and reflex activity and there will be a lack of evidence of intra-abdominal disease; in the latter no evidence of disease of the nervous system will be found.

Weakness may occur in diseases of other organs than the nervous system. Many times a diagnosis of infantile paralysis has been made during an epidemic, in children suffering from rickets and scurvy producing a pseudo-paralysis. It is important also to note that failure of movement because of pain is not a paralysis. Not infrequently an arm or leg has been said to be paralyzed when it was not moved only because of pain. A tuberculous hip joint has often led to this error.

In occlusion of the leg arteries, from arteriosclerosis or thromboangiitis an intermittent halt or claudication occurs in which the patient after walking a short distance finds it less and less possible to move the legs and finally must rest for a time, before he is again able to resume as before. The characteristic position of the hands and feet in carpopedal spasm occurring in spasmophilia and tetany, as well as the increased irritability of nerves and muscles should differentiate this condition from paralysis. The asthenia due to Addison's disease should not be confused with myasthenia gravis. Certain forms of polyarthritis are associated with a degree of muscular atrophy and weakness simulating neurologic disease. Sensory loss and reaction of degeneration are always absent.

Pupillary inequality due to unilateral paralysis of the cervical sympathetics as the result of apical pleurisy or lesions in the neck should not be interpreted as an indication of disease of the central nervous system.

From this rather disjointed catalogue one may discern the inseparability of neurology from medicine and conclude only that the practice of medicine is the practice of neurology.

MACROCYTIC ANEMIA IN BANTI'S DISEASE *

By D. O. Wright, *New Orleans, Louisiana*

An enormous literature has accumulated since Banti first described the three-stage syndrome to which his name has become the eponym. In reviewing countless descriptions that have appeared throughout the years, one finds the almost universal, and at times dogmatic, statement that the accompanying anemia is of the normo- or microcytic type.

A case of Banti's disease which shifted while under observation from a microcytic hypochromic type of anemia to one that closely resembled pernicious anemia during remission, has emphasized the fallibility of this statement. The purpose of this communication is to call attention to and suggest a possible explanation for this very definite metamorphosis.

Case Report

F. B., a white male, aged 35, was first admitted to the ward October 9, 1933, complaining chiefly of universal pruritus. General malaise, lassitude and some slight loss of weight had been more or less progressive for at least a year. Two or three months before admission jaundice and pruritus made their appearance. His past and family histories revealed no relevant facts. He was a man of good development but only in a fair state of nutrition. He had a very slight icteric tinge to the sclerae. Blood pressure was 126 systolic and 80 diastolic; pulse 80; respiration 16; temperature 98°. The liver was palpable 2 or 3 cm. below the costal margin. The spleen was enlarged and very firm, extending almost to the umbilicus. A gastrointestinal roentgen series failed to indicate any gastric lesion other than pressure due to the enlarged spleen. Blood chemical tests were within normal limits. The Wassermann test was negative. The fragility test was within normal limits. Urinalysis showed: sp. gr. 1.022, trace of bile, occasional pus cell and hyaline cast. The blood picture at this time showed:

R.B.C.	4,535,000
W.B.C.	4,000
Hgb.	65%
C.I.	0.72
M.C.V.†	68 cubic microns

He was discharged 10 days after admission. During the following two or three months jaundice was absent, he gained 18 pounds and was feeling much better in general. In February 1934 he began to lose strength and weight rather rapidly. There was some swelling of the abdomen which varied from time to time and jaundice reappeared. He was re-admitted to the ward March 26, 1934, with moderate amount of free fluid in the abdomen. The liver had increased in size considerably and was quite hard. The spleen reached almost to the umbilicus. At this time the blood count, showing a definite change from a micro- to a macrocytic anemia, was as follows:

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† Mean Corpuscular Volume—Volume of packed red cells expressed in cubic centimeters per 1000 c.c. of blood, divided by the number of red cells expressed in millions per cu. mm.; an index of the mean size of red cells, the normal being 75–85 cubic microns.[1]

R.B.C.	4,665,000 *
W.B.C.	4,000
Hgb.	103%
C.I.	1.11
M.C.V.	99

The fragility test was repeated and found to be normal. The van den Bergh test gave a direct and immediate positive. Splenectomy was performed March 17, 1934. A note was made at operation that "the spleen was over the midline and down to the umbilicus. The liver was congested (hobnail type). Free liver edge was moderately rounded. The vessels in the omentum were large and engorged." Microscopic diagnosis, "moderate hyperplasia of the pulp with diffuse fibrosis, chronic splenic tumor compatible with Banti's disease."

On discharge the patient was greatly improved. There was no further ascites. The blood count made immediately before discharge from the hospital showed no appreciable change from the count on admission.

Review of Literature

The not infrequent appearance of a slight macrocytosis and a high color index with portal cirrhosis has been widely recognized. Wintrobe and Shumacker,[2] Van Duyn,[3] Goldhamer,[4] Schulten and Malamos [5] have recently called attention to this interesting phenomenon. A review of the less recent literature is included in the article by Wintrobe and Shumacker. In a recent communication [6] I reported the blood pictures of 12 cases of portal cirrhosis and reviewed the records of 41 additional cases. The name pernicioid (pernicious-like anemia) was suggested for this interesting condition. This descriptive term will be used in the discussion that follows.

Twenty-seven and four-tenths per cent of the 41 case records of portal cirrhosis which I reviewed showed a color index of 1 or more, and 18 per cent of the cases reviewed by Van Duyn had a color index of more than unity. Since a portal cirrhosis characterized the end stage of Banti's disease it would not be too bold to anticipate a macrocytic blood picture if and when the portal cirrhosis has progressed sufficiently.

Hanrahan [7] reported 35 cases of splenic anemia. If his cases with ascites as well as those diagnosed cirrhosis at autopsy or operation are considered to have cirrhosis, this forms a group of eight whose average color index is .89. Three of these patients, or 37.5 per cent, had a color index of more than 1. In the remaining 26 cases (one has been excluded), which were without definite evidence of cirrhosis, only 11.6 per cent had a color index of 1 or more. The average color index of this group was .68, as contrasted with the color index of .89 of the cirrhotic group. The following pertinent observation made by Hanrahan is quite interesting: "We have seen how the approach to the pernicious type of anemia is marked by increasingly poor prognosis." The case omitted was one that showed a normal blood picture except for a color index of more than 1 when observed 25 years after splenectomy.

* A series of subsequent blood counts showed no essential change from this count.

Report of 37 Case Records

The Charity Hospital records have been reviewed in an endeavor to substantiate the hypothesis that a macrocytic anemia develops in Banti's disease when liver cirrhosis develops. Thirty-seven records of Banti's disease were reviewed. All cases showing a positive Wassermann or any other possible etiologic factor were excluded. Nearly all of these patients had applied for admission late in the course of their illness as evidenced by the fact that 22 had a demonstrable amount of free fluid in the abdominal cavity at some time during their stay in the ward. A diagnosis of Banti's disease with cirrhosis was made on three other patients at autopsy or operation, forming a group of 25 with definite evidence of portal cirrhosis. Sixty per cent of this group had a color index of 1 or more, the average for the group being 1.04. Only 25 per cent of the remaining cases, which did not have definite evidence of cirrhosis, showed a color index of 1 or more. The mean color index for this group was much higher than one would expect, it being 0.92. This can be explained by the fact that their histories had been of long duration. Seventy-five per cent of this group had suggestive indications of portal cirrhosis, namely a palpable liver or a history of hematemesis extending over a period of several years.

The average age for the entire group was 31.8.

Gastric analysis was recorded in eight cases. Four out of this eight showed an absence of free hydrochloric acid.

Summary and Conclusions

A case of a patient with Banti's disease is reported whose blood count showed a very definite change from a hypochromic microcytic type of anemia to a macrocytic type closely resembling pernicious anemia in the stage of remission.

A series of cases diagnosed as Banti's disease have been analyzed to show that a color index of greater than unity is much more frequent and the mean color index higher in the groups with evidence of portal cirrhosis than in those without this complication.

It is a well substantiated fact that a macrocytic type of anemia frequently occurs in portal cirrhosis. From this case report and from a study of a series of cases of Banti's disease it is obvious that a macrocytic (pernicioid) type of blood picture will appear when portal cirrhosis develops. The concept that Banti's disease is always accompanied by a microcytic type of anemia is erroneous.

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ALKALOSIS, A CLINICAL PROBLEM *

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ALKALOSIS is a term applied to that condition of the acid-base balance of the blood in which the concentration of the blood bicarbonate is above the normal level. It may be more broadly defined as an abnormal condition caused by the accumulation in the body of an excess of alkali or by the loss of acid. Alkalosis has been observed clinically in a number of conditions, but has, however, been most frequently encountered in cases on Sippy management or in cases with pyloric or upper intestinal obstruction accompanied by vomiting. It is not the purpose of this report to consider the subject of alkalosis as it applies to clinical medicine in a general way, but to present a number of cases of hypertensive and renal disease in which an alkalosis was encountered.

Nephritis with nitrogen retention has generally been considered to be associated with a progressive acidosis. Whitney [1] and Chace and Myers [2] were among the first to point this out. The latter workers observed that all fatal cases of chronic nephritis with marked nitrogen retention showed a severe acidosis, sufficient in many instances to be the actual cause of death. Since acidosis is a term applied to conditions in which the bicarbonate concentration of the blood is lowered, it may arise from several causes; a reduction of the total base concentration of the blood or an increase of the acid ions. An influx of acid into the blood may occur from an abnormal formation as in diabetes mellitus or from a decreased elimination as in chronic nephritis. As to the retained acid, various workers have ascribed considerable importance on the one hand to a retention of phosphate,[3] and on the other hand to a retention of sulphate.[4] Recently considerable attention has been given to a lowering of the plasma total base concentration.[5]

About six years ago a study was begun with the object of observing the progressive changes of the acid-base balance of the blood in cases of hypertension and various types of renal disease. It was the aim in this study to obtain the blood as early in the disease as possible and then to follow the changes until termination. One of the first cases observed, clinically, appeared to be in a condition of acidosis. The nitrogen retention was only slight and the blood pressure was markedly elevated. To our surprise the bicarbonate concentration of the blood was not lowered but was at the upper normal or even slightly above. Interest was immediately aroused as to whether this was an exceptional finding or that perhaps it occurred occasionally in cases showing relatively little nitrogen retention but having a marked elevation in blood pressure.

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.
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To date an acid-base balance study of the blood has been made of some 90 cases showing hypertension and renal disease of different types. Forty-five of these were cases showing marked elevations in blood pressure with only relatively little nitrogen retention. It is in this group of cases that the finding was made, of a tendency to an elevation of the plasma pH and bicarbonate content, which at the same time was accompanied by a tendency towards a lowered plasma chloride concentration.

Table 1 presents data of the acid-base balance of the plasma of three somewhat typical cases showing marked nitrogen retention. Since the blood

TABLE I

The Acid-Base Balance of the Plasma in Renal Disease with Nitrogen Retention

Case No.	Date	Plasma					Urea Nitrogen
		pH	CO_2	NaCl	Protein	Total Base	
			Vol. %	Mg./100 c.c.	Gm. %	m. Eq.	Mg./100 c.c.
1	3/11/30	7.28	26.5	569	6.3	138.2	105 N.P.N.
	4/ 4/30	7.18	24.9	575	6.6	140.0	160 " " "
	4/15/30	7.09	29.8	536	7.2	135.8	
2	3/24/30	7.41	37.7	582	6.6	137.8	170 " " "
	3/31/30	7.23	38.7	556	7.1	138.7	169 " " "
	4/15/30	7.19	34.7	535	7.4	138.8	
	4/28/30	7.29	27.4	522	7.0	143.6	240 " " "
3	11/13/29	7.44	63.2	616	3.6	150.8	13
	3/31/30	7.43	60.0	606	4.2	143.4	12
	10/28/32	7.30	49.0	647	5.6		25
	11/16/32	7.33	43.2	626	5.8	148.3	95
	12/28/32	7.37	38.6	616	5.6	152.0	
	1/ 6/33	7.30	30.4	576		146.9	146
	1/20/33	7.28	32.4	488	6.0	146.7	

findings of these cases are more or less typical of renal disease with nitrogen retention the cases will not be reviewed in detail. Cases 1 and 2 were clinically chronic glomerulo-nephritis, with terminal uremia. Case 3 was early the nephrotic type of acute nephritis, and terminated, as was confirmed at post mortem, a chronic glomerulo-nephritis. It is observed that both the pH and CO_2 are lowered and at the same time the final blood shows a definite lowering of the plasma chloride. The total base also tends to be lowered. In Case 3 attention should be called to the marked loss of chloride which occurred at termination. The patient experienced considerable vomiting. In fact the nausea and vomiting were so severe that no food could be taken for several days at a time. With this marked loss in plasma chloride the bicarbonate did not increase, as occurs in the vomiting from pyloric obstruction, but remained lowered. It should also be observed in this case that when the blood urea became elevated the bicarbonate had a tendency to fall.

Table 2 shows, in contrast, the change of the acid-base balance which may be observed in patients with a marked elevation in blood pressure and relatively little nitrogen retention.

TABLE II

The Acid-Base Balance in Cases of Persistent Hypertension

Case No.	Date	Plasma					Urea Nitrogen
		pH	CO_2	NaCl	Protein	Total Base	
			Vol. %	Mg./100 c.c.	Gm. %	m. Eq.	Mg./100 c.c.
4	9/12/28	7.45	66.0	562	6.3	146	13
	2/ 7/29	7.54	69.1	521	6.4	140	
	2/15/29	7.54	84.6	497	6.0		
	2/23/29	7.56	84.2	492	6.5		64 N.P.N.
	3/ 1/29	7.54	79.4	492	6.4		39 " " "
	3/ 9/29	7.56	81.2	486	6.0	137	
5	9/19/28	7.39	60.5	596	5.6	156	23
	10/ 9/28	7.52	66.8	544	6.0	142	
	10/24/28	7.41	80.9	497	5.9	140	
6	2/13/30	7.56	72.7	550	6.1	142	
	2/19/30	7.59	73.6	532	6.6		30 N.P.N.
	3/14/30	7.54	69.4	532	6.7	140	32

Case 4. T. W., female, aged 38, housewife, was observed over approximately two and one-half years. Her chief complaints were headaches, accompanied by nausea and vomiting, throbbing in the head, numbness and tingling in extremities, progressive weight loss and nocturia. During the latter period of her illness vision was seriously impaired.

The salient physical and laboratory findings were slight cardiac enlargement, systolic blood pressure which varied from 180 to 260, and diastolic pressure from 130 to 160; the fundi of both eyes showed arteriosclerotic changes; the uterus was about the size of a grapefruit, firm and apparently fibroid in nature; the urine showed a trace of protein during the last year of observation with occasional hyaline and granular casts; serological studies of both blood and spinal fluid were negative; complete gastrointestinal roentgen-ray findings were negative.

During the latter part of this patient's illness her most distressing problems were headache and vomiting, from which it was almost impossible to afford any effective relief. Consequently weight loss was very marked. During the last week of life typical carpo-pedal spasm was observed. A period of stupor of about two days' duration preceded death. Clinical diagnosis: Malignant hypertension; alkalosis; and slight cardiac hypertrophy.

It is seen that the plasma pH and bicarbonate content are definitely elevated and at the same time the plasma chloride is markedly lowered. It is interesting that the urine remained acid despite the elevated bicarbonate of the blood.

Case 5. J. A. W., male, aged 24, bookkeeper, was first seen 7/17/28, at which time his chief complaints were headaches, periodic in nature, occasionally accompanied by nausea and vomiting; slight swelling of both ankles; spots before the eyes; and nocturia two or three times a night.

History revealed a severe scarlet fever four years previous, several attacks of acute tonsillitis, appendectomy in 1918 and tonsillectomy in 1922.

A period of hospitalization at this time resulted in the following findings; albuminuric retinitis, slight cardiac enlargement, slight edema of both ankles, systolic blood pressure varied between 232 and 190 and diastolic varied from 160 to 120. Modified Mosenthal test showed a practically fixed specific gravity at a low level. Variations in day specimens were between 1.010 and 1.014. The night quantity from 8 p.m. to 8 a.m. showed a volume of 995 c.c. and a specific gravity of 1.010. Urine analysis showed a trace of protein and numerous hyaline and finely granular casts, a few erythrocytes and a few leukocytes.

On 8/16/28, approximately a month after first examination, after a very severe headache, patient was taken with convulsions and for three days remained in a stuporous state. Blood pressure was 200 systolic, 120 diastolic at this time. With usual therapeutic measures, he gradually improved and was able to leave the hospital in three weeks. During this time the highest blood urea N observed was 28.5 mg. and creatinine was 4.1 mg. Phenolsulphonephthalein excretion was 32 per cent in two hours. The final acid-base study was made just two days before death. The patient became progressively weaker and died 10/26/28 in coma. Clinical diagnosis: Chronic glomerulo-nephritis, slight cardiac hypertrophy.

Here again, as with the following Case 6, the pH and CO_2 are elevated while the chloride is lowered.

Case 6. M. H., female, white, aged 46, housewife. Present illness was of six years' duration, during which time the main symptoms were severe and frequent headaches, frequency of urination day and night, and weight loss. At the time the patient came under our observation, which was 50 days before death, there was some shortness of breath and cough on exertion. With bed rest these symptoms largely disappeared. Three days before death, the patient lapsed into a comatose state, accompanied by Cheyne Stokes respiration. Death occurred in this condition on 3/28/30. Past history revealed no severe illnesses, nor operations; six pregnancies, one still birth, one child died at five years, four children living and well.

Physical examination revealed a well developed but poorly nourished white female. Heart was moderately enlarged in all diameters without clinical valvular disease. Lungs showed a small amount of basal moisture, bilateral, which cleared with bed rest. Liver was just palpated below costal margin, firm but slightly tender. Blood pressure varied from 270 to 228 systolic and 170 to 150 diastolic. Eye grounds showed marked sclerosis of retinal vessels. Laboratory findings: urine showed a heavy trace of protein and numerous hyaline and granular casts, an occasional red blood cell and leukocyte. Blood N. P. N. was 30.4 and 31.8. No alkali was administered at any time during the period of observation. Blood chemical studies here reported were made 2/13/30, 2/19/30 and 3/14/30, the last observation just two weeks before death occurred. When the blood samples were taken, signs of cardiac failure were not present in an appreciable degree.

Final pathological diagnosis: Arteriolosclerosis of kidneys, spleen, pancreas and suprarenals. Nephrosclerosis, marked, with multiple small hemorrhagic infarctions and hemorrhagic arterionecrosis. Discrete endarteritis of pancreatic arterioles with focal necrosis. Hypertrophy and dilation of heart. Multiple small anemic infarctions of myocardium. Multiple mural thrombi of both ventricles and right auricle. Multiple hemorrhagic infarctions of both lungs. Chronic passive congestion of liver, spleen and small intestine. Kidneys together weighed 226 grams.

To date we have observed about 12 such cases, wherein similar results were obtained. Of course the elevation of bicarbonate in all instances was not as great as in Case 4, however all of these 12 showed the blood bicarbonate concentration to be at the upper normal or above.

It has been our experience that it is a rather common procedure among

practicing physicians to recommend the administration of alkalies to patients with renal disease showing some clinical signs of an existing acidosis and to employ the reaction of the urine as a guide to therapy. It should be emphasized at the outset that the promiscuous use of alkalies in such cases is in certain instances irrational. That is, some cases are apparently not able to handle excess alkali as well as others. This observation is of course not new. In 1917, Palmer and Van Slyke [6] showed that in normal individuals the urine changes alkaline after the administration of bicarbonate when the plasma CO_2 reaches 71 ± 5 vol. per cent. It was pointed out by them, however, that in pathological cases this level of bicarbonate is not so well defined, and there is a danger of giving unnecessary and perhaps injurious amounts of bicarbonate if continued until the urine turns alkaline. Myers and Booher [7] have reported two cases in which the urine remained strongly acid despite the development of an alkalosis. It is interesting that Case 4 excreted an acid urine despite the markedly elevated blood bicarbonate concentration.

Recently two cases have come under our observation which had been receiving alkali and in whom a definite alkalosis existed. Table 3 presents the observations on these two cases.

TABLE III

The Acid-Base Balance of the Plasma in Renal Disease

Case No.	Date	Plasma					Urea Nitrogen
		pH	CO_2	NaCl	Protein	Total Base	
			Vol. %	Mg./100 c.c.	Gm./100 c.c.	m. Eq.	Mg./100 c.c.
7	2/29/32	7.50	77.5	529	6.3	159.0	
	3/ 1/32	7 47	87.6				
	3/ 8/32	7.50	68.1	548	6.7	154.0	
	3/18/32	7.39	47.5	570	6.7	146.0	182
	3/25/32	7.17	27.2	575	7.4	154.0	150
8	3/ 8/33	7.50	87.5	502	6.9	166.0	
	4/24/33	7.46	74.5	533	8.2		
	5/13/33	7.46	68.6	580	8.1	151.0	35 N.P.N.
	7/14/33	7.44	61.0	566	7.3	147.0	35 " " "
	2/ 1/34	7.46	68.4	562	7.0		

Case 7. C. T., male, white, age 42, was admitted to the hospital February 26, 1932, died March 26, 1932. Subsequent to his war experience in 1918, at which time he developed bacillary dysentery, he suffered from severe constipation and spastic colitis. Four years previous, following operation for hemorrhoids, he had an acute cystitis, proctitis, colitis and prostatic abscess. The latter ruptured into the rectum with sinus formation. Shortly after, he showed protein and formed elements in the urine and was considered to have an ascending pyelonephritis. Known hypertension existed for two years, and one year before, there was complete right hemiplegia. His chief complaints were severe throbbing headaches, nausea and vomiting, con-

stipation, frequency and burning on urination, progressive weakness and 58 pounds weight loss during the last year. In Dec. 1931 he visited the Mayo Clinic and Dr. Norman Keith kindly sent the following report of their findings. "He registered at the Clinic on December 16, 1931, and at that time we felt that he had a serious form of general arterial hypertensive disease. In addition to having the picture of so-called malignant hypertension in the eye grounds, there was some evidence of mild renal insufficiency. There was some myocardial degeneration, but no actual decompensation at that time. The urologic examination revealed a moderate amount of chronic, non-specific prostatitis which is probably secondary to the colon bacillus; the urinary culture yielded the colon bacillus."

Physical examination on admission to the hospital revealed a pale, markedly emaciated white male, with slight dyspnea. Weakness of right facial and orbital muscles was evident. Heart was enlarged 2 cm. to left of mid-clavicular line. Lungs were clear; liver and spleen not palpable. Peripheral vessels were markedly sclerosed. Blood pressure was 240 systolic and 165 diastolic. Red blood cells 3,180,000, white blood cells 8,600, hemoglobin 65 per cent. Urine analysis: specific gravity 1.010; protein in moderate amount; a few casts; many leukocytes and a few red blood cells; phenolsulphonephthalein output February 29 showed 15 per cent the first hour and 20 per cent the second, total of 35 per cent in two hours. Standard urea clearance: February 2—14 per cent, February 5—12 per cent of normal.

Hospital management: Alkaline ash diet was ordered on February 27. On March 3 diet was changed to one of low protein. Triple bromide, grains 15, was ordered on February 28 and the patient had received 10 of these tablets prior to our first blood chemical study on February 29. These were continued to March 5. Beginning March 3, ammonium chloride grains 10, three times daily, was given for a brief period to counteract alkalosis. On March 19 patient was transfused to which he reacted poorly, and developed acidosis, lapsed into coma and died in a uremic state.

Case 8. R. W., male, white, age 14, has been observed from 2/27/33 to date. He was hospitalized from 2/27/33 to 3/16/33 at which time the following history and findings were obtained. Five days before admission to hospital, onset of acute symptoms of present illness occurred, which were headache, backache, indigestion, and finally just before hospitalization a generalized convulsion. Past illness included measles, whooping cough and chicken pox. Previous to onset of present illness there was a history of nocturia and daily frequency, and a 10 pound weight loss during the last year.

Physical examination revealed an undernourished boy in a stuporous state. Heart was slightly enlarged and showed a pericardial friction rub. The blood-pressure was 176 systolic and 140 diastolic. Temperature varied from 37.5° C. to 38.8° during the 18 days of hospitalization. The urine showed a trace to heavy trace of protein, occasional granular cast and an occasional red blood cell and leukocyte. Blood count: red blood cells 3,950,000, white blood cells 15,500. Blood urea N 25.8. Creatinine 1.6.

For a period of 10 days preceding the first acid-base study 8 gm. of citrocarbonate were given three or four times a day upon the clinical assumption that the picture was one of acidosis. Subsequent acid-base studies were made without the exhibition of any alkali.

Diagnosis: Acute exacerbation of chronic glomerulo-nephritis.

During the past year there has been some gain in weight and some clinical improvement. Blood pressure, however, has persisted high; in January 1934 it was 190 systolic and 145 diastolic.

It is observed from table 3 that the pH and plasma bicarbonate content were markedly elevated at the time of the first observation. The chloride

concentration on the other hand was definitely lowered. Case 7 was given ammonium chloride for a short period. During this period the bicarbonate was decreased and the chloride was increased somewhat. As stated in the case review, he was transfused and reacted poorly. The terminal blood showed an uncompensated acidosis. Case 8 received no ammonium chloride. The alkalies were discontinued and a moderate amount of salt was given in his diet. The pH and CO_2 fell to within the normal range and the chloride increased to a lower normal value.

In conclusion we feel justified in stating that cases of hypertension and renal disease presenting a markedly elevated blood pressure with only slight, if any, increase in the blood non-protein nitrogen constituents, may show a shift in the acid-base balance of the blood, which is characterized by a tendency toward an elevated pH and bicarbonate content and a lowered chloride content.

The administration of alkali should be gauged by analyses of the plasma CO_2, since apparently some cases are not able to handle excess alkali as well as others, and further since the distinction between acidosis and alkalosis clinically is in some cases rather hard to make. The promiscuous administration of alkali should be discouraged unless carefully controlled by blood acid-base analyses.

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OBSERVATIONS OF REMISSIONS IN HYPERTHYROIDISM INDUCED BY PREGNANCY URINE EXTRACT *

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Two years ago the administration of pregnancy urine extract (Antuitrin S) † to patients with hyperthyroidism was begun in this Clinic.‡ A summary of metabolic results has been reported.[1] In some patients a rapid remission occurred. The thyroid status of these patients a year or more later is to be given in this paper together with brief clinical descriptions. Six new case reports are presented. The characteristics of those patients in whom remission was not induced will be analyzed. The 13 patients are divided into four groups. Treatment consisted of one cubic centimeter of Antuitrin S (100 R. U.) or of Theelin (50 R. U.) given subcutaneously daily or three times a week for specified periods before or after menses as indicated. Antuitrin S is referred to as P. U. E.

GROUP I

Three patients of a type now thought to be unsuitable for pregnancy urine extract treatment were observed during the summer and fall of 1932. The results in these patients have been reported. The group is composed of two older women and a boy of 17 years.

Case 1. A woman, Mrs. G. M., 53 years old, whose last menses had occurred two years before, was admitted to the Clinic in August 1932. She had lost 39 pounds in the last five years, during which time she had been nervous and easily excited.

On examination the pulse rate was 112, regular; she had a moderately enlarged, firm goiter. The basal metabolic rate in August 1932, was + 30 per cent. She was given P. U. E. and Theelin alternately, daily for three months. During this time no menstruation occurred and the basal metabolic rate was not significantly altered. The final reading, before operative treatment in December 1932, was again + 30 per cent.

Case 2. Mrs. L. S., 46 years old, had had a goiter for 23 years. She was still menstruating regularly. She had been conscious of palpitation and increasing nervousness for two years.

On examination a vascular hypertension (190–100), a nodular goiter and a fine tremor of the hands were found, but no exophthalmos. Before treatment the basal metabolic rate was + 39 per cent and + 37 per cent on two occasions. P. U. E. was given after the menses in October, followed by Theelin for two weeks, and P. U. E. again three times a week during the month of November. Menstruation in November was delayed. Following a temporary drop, a rise in metabolic rate occurred during January and February, the fourth and fifth months of observation. Following the menses in January, P. U. E. was given daily for two weeks and the metabolism rose to + 53 per cent. Operative treatment was then successfully carried out.

Case 3. E. A., a boy 17 years old, whose mother had had hyperthyroidism, came

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† Generously furnished by Dr. E. A. Sharp, Parke, Davis & Company.
‡ From the Thyroid Clinic, Northwestern University Medical School, Chicago.

to the clinic in November 1932. He had developed a typical exophthalmic goiter following an upper respiratory infection six months before admission.

On examination he had slight exophthalmos, tremor, weakness, and a small, diffuse goiter. The pulse rate was only 84. The basal metabolic rate was + 36, + 39 and + 54 per cent on successive determinations before treatment. He was given P. U. E. three times a week for five months. After the first month of treatment a transient remission occurred (basal metabolic rate + 11 per cent). This was soon followed by a recurrence; at the end of treatment the metabolic rate was + 26 per cent. There had been a 10 pound gain in weight but clinically no diminution of the hyperthyroidism had occurred.

Group II

Two very mild cases were first treated in the spring and summer of 1932.

Case 4. A thin, nervous girl of 19 years, whose mother has a goiter, was examined in April 1932. Goiter was first noted at 14 years of age. She had been nervous for three years; had always been thin; had lost from 108 to 103 pounds; she had never had cardiac palpitation until three months before examination. She felt warm, perspired freely, had noted weakness and shakiness of her legs. The menses had been irregular, occurring at intervals of from six weeks to two months. Amenorrhea for four months had occurred once. She had bilateral headache before menses. This history suggested hyperthyroidism with failure of ovarian function to become predominant in the third phase of puberty.

Examination found a thin, easily excited girl with considerable symmetrical goiter, pulse 140; bright eyes without definite exophthalmos, and a fine tremor. The heart and lungs were normal. Four basal metabolic rates during a control period of seven weeks were + 19, + 15, + 10 and + 16 per cent. The average weight was 99 pounds; pulse average 108.

Treatment was started 26 days after the preceding menstrual period; it consisted of eight injections of P. U. E. given in a period of 15 days. Menstruation occurred after the first two doses. Injections were continued through and for eight days after menses.

Result: The three basal metabolic rates during a six week period immediately following this 15 day course of injections were — 6, — 4, and — 14 per cent, with weight rising to 103 pounds and pulse averaging 82.

Subsequent observations from August 1932 to December 1933, 18 months from treatment, found a basal metabolic rate average of — 8.5 per cent, with weight range from 101.5 to 104.5 pounds, and pulse range from 72 to 96. Menstruation occurs regularly every 30 days and lasts four days. The goiter is diffuse and somewhat smaller. Her nervous temperament seems about the same but thyrotoxic symptoms of tremor, tachycardia and muscular weakness are absent.

Case 5. A Polish woman, 33 years of age, whose youngest child was a year old, reported to the clinic in August 1932. She complained of nervousness, weakness, palpitation and tremor. On examination there were no exophthalmic signs but marked tremor and a diffuse, small goiter without bruit were found. The basal metabolic rate was + 29 per cent, pulse 90, weight 110 pounds.

Treatment: One cubic centimeter of P. U. E. was given subcutaneously three times a week for eight weeks. During treatment two regular menstrual periods occurred; three basal metabolic rates during this time averaged + 19 per cent. Two weeks following treatment the metabolic rate was + 13 per cent; after four weeks it was + 6 per cent, and for five months ranged from + 5 to — 8 per cent; she gained eight pounds in weight and the pulse rate dropped from 90 to 76. Clinically she became non-toxic and undertook factory work.

Two moderately severe cases of hyperthyroidism in young women were then treated.

Case 6. An unmarried Italian immigrant girl, 17 years of age, was admitted to the clinic in September 1932. She had come to Chicago when she was seven years of age. A goiter was noted three years later. She complained, on admission, of weakness, nervousness, excessive sweating, difficulty in climbing stairs due to weakness of her legs, and slight loss of weight. She stated that menses of four days' duration occurred every 28 days.

On examination the pulse was regular, very fast, 144; there were marked tremor, excessive sweating; no exophthalmic eye signs; a small, smooth, symmetrical goiter. Two basal metabolic rates before treatment were + 67 and + 34 per cent; weight average 120 pounds, pulse average 118.

Treatment was given for seven weeks from September 16 to November 7, 1932, consisting of P. U. E. given for one week after three successive menses, and Theelin given for two weeks preceding the second and third menses.

The result of treatment in this case was extremely dramatic in contrast to the preceding and subsequent cases. The metabolic rate during the seven weeks' treatment progressively dropped to + 3 per cent; the weight increased 20 pounds; the pulse dropped to 96. Clinical signs of toxicity disappeared. She seemed phlegmatic.

Subsequent observations have found her in a steady state as regards basal metabolism. Tests during 13 months' observation have been — 2, ± 0, — 4, and — 4 per cent; weight average 139 pounds; pulse from 72 to 88. She is doing factory work. The goiter which was not large at any time seems unchanged by gross clinical observation.

Case 7. A married German girl of 22 years entered the clinic on January 5, 1933. She had delivered her first child in May 1931; eight months later, in January 1932, she noted a goiter and she became extremely irritable. Separation from her husband occurred at this time. She lost 36 pounds in weight. Partial recovery from this apparent acute hyperthyroidism occurred during 1932, evidenced by gain in weight, but she still complained of nervousness, irritability and weakness.

On examination the pulse was 110; there were marked tremor, slight sweating, slight definite exophthalmos, a soft, diffuse pulsating goiter giving a bruit. The basal metabolic rates for three weeks in January 1933, before treatment, were + 34, + 53, and + 49 per cent; pulse average 138; weight 136 pounds.

Treatment was given for one week before the menses in February and March 1933. One week after menstruation in March the metabolic rate was + 15 per cent, pulse 96, weight 142 pounds. This sudden remission, similar to that in Case 6, was, however, not maintained, and in April the metabolic rate rose to + 33 per cent. P. U. E. had been given in March and after the menses in April. Subsequently, however, with further administration of P. U. E. during May and June, the basal metabolic rate dropped to + 2 per cent in July 1933, and since then for nine months the patient has been in a steady metabolic state with readings of + 7, + 6, ± 0, + 5 per cent, and in April 1934, — 10 per cent. For six months she has been working hard and long as a general housemaid.

Group III

In contrast to these four very successfully treated patients, the three succeeding patients were not benefited. These cases have not previously been reported.

Case 8. Mrs. M. P., 34 years of age, entered the clinic in January 1933. She had lost 48 pounds in weight, from 198 to 150 pounds, in the preceding three months.

On examination the pulse was 108; there were marked tremor, no exophthalmic signs, a smooth, soft goiter without bruit. The basal metabolic rates before treatment were + 58, + 44, and + 41 per cent; pulse 108, weight 150 pounds.

P. U. E. given before menses in February and March led to a drop in metabolic rate to + 16 per cent, with a pulse of 76, weight 156 pounds. This marked remission, however, was not maintained. During April an upper respiratory infection occurred and in spite of two further courses of P. U. E. the metabolic rate rose to + 57, + 53 and + 56 per cent.

Case 9. Mrs. M. M., 30 years of age, presented herself at the clinic on May 23, 1933. She had had a pelvic infection after marriage at 17 years of age, and had had two pelvic operations at 23 and 24 years, in one of which the right ovary had been removed. Menses, since these operations, had been regular but of only one day duration. Her complaint was of fatigue, tachycardia, sweating, occasional diarrhea, and loss of 15 pounds in weight.

On examination the pulse rate was 120; she had a fine tremor, and a small thyroid enlargement on the right, with no other definite signs. The basal metabolic rates during three weeks of observation were + 44, + 36 and + 40 per cent; average weight 141 pounds, pulse average 108. P. U. E. was given for three weeks after menses, Theelin for one week before the next menstrual period, and P. U. E. again for 12 days after it. During this month the basal metabolic rate rose to + 53 and + 55 per cent. Not even the temporary remission that had occurred in other unsuccessful cases was present in this. Lugol's solution was then started and in turn failed to reduce the metabolic rate, but following thyroidectomy this determination was — 8 per cent, and marked clinical improvement occurred.

Case 10. M. C., a negress, 25 years of age, came to Chicago from Mississippi six years ago. A year later she delivered a child which lived six months; two miscarriages occurred subsequently. Her complaint was of blurring of vision, nervousness, marked loss of weight, and excessive weakness. She presented on examination an ophthalmoplegia and such marked muscular weakness as to suggest myasthenia gravis. The thyroid was considerably enlarged, tense, not nodular, and had no bruit. The basal metabolic rate was + 50 and + 51 per cent; weight average 138 pounds, pulse rate average 114.

Theelin and P. U. E. were given for three months with no effect on the metabolic rate.

Group IV

The three cases in this group are still under observation. They have had marked clinical improvement but are not entirely free of hyperthyroidism as indicated by the basal metabolic rate.

Case 11. A married woman (Mrs. L. O'R.), 41 years of age, reported to the Clinic on July 11, 1933. For two years she had had nervousness, tremor, sweating, increased appetite and emotional irritability. Her menses had usually been of three days' duration but had been decreasing and had been absent for four months. She had never had a goiter.

On examination she was found to have a very marked tremor, slight failure of convergence of the eyes, a slight enlargement of the thyroid, and a pulse of 120. Two metabolic rate tests during a three weeks' control period were + 65 and + 50 per cent, with pulse average of 118, and weight average of 124 pounds.

Treatment, in the absence of menses, was begun with Theelin, 1 c.c. every other day for four weeks. Menses occurred and P. U. E. was given three times a week following this period for two weeks. The basal metabolic rate at the end of this time was + 23 per cent, pulse 115, and weight 127 pounds. For the next three

months Theelin and P. U. E. were used alternately. Another irregular menstrual period occurred. Following this the basal metabolic rate was + 10 per cent, pulse 83, weight 131 pounds. A clinical cure seemed in progress, but during the next four months, although the weight has steadily increased to 140 pounds, a gain of 16 pounds, and has been maintained, the basal metabolic rate has risen to an average of + 25 per cent, and the pulse to 100. No menses have now occurred for three months.

Case 12. A married woman of 38 years (Mrs. W. B.) came under observation on December 11, 1933. Her complaint was that for four months she had had marked weakness, tremor, nervousness and sweating. Three day menses were at a 23 day interval.

On examination she appeared exceedingly thyrotoxic. There was very marked tremor, extreme quadriceps weakness; a regular pulse of 130, no definite exophthalmos, and a diffuse, firm goiter without a bruit. Three metabolic rate measurements before treatment were + 61, + 58, and + 51 per cent, with average weight of 107.5 pounds, and average pulse of 122.

P. U. E. was given daily for three weeks; then for one month P. U. E. and Theelin were given alternately daily; after the second menses during treatment P. U. E. was given daily for eight days. During this course of treatment there was no definite improvement although the metabolic rate declined to + 40 per cent, the pulse average to 118, and the weight decreased to 105. The next menstrual period was delayed two weeks. A normal flow then occurred. At this time a definite transition toward recovery began. The weight began to rise steadily; muscular strength increased; the pulse rate and metabolic rate dropped progressively. The last metabolic rate, after five months of treatment, was + 15 per cent, pulse 86, weight 118 pounds —a gain of 13 pounds. P. U. E. has been given after each of the last three menses occurring since the delayed flow in February. The patient is now doing her own sewing and other housework, and feels in nearly normal health. This is the most severely thyrotoxic patient we have treated.

Case 13. Mrs. L. P., 35 years of age, married, of Russian nationality, was admitted to the clinic on October 4, 1933. Her second marriage (of four years' duration) was a happy one. There have been no pregnancies. Dr. B. F. Heskett reported an infantile uterus. Her complaint was of fatigue, cardiac consciousness, nervousness and tremor. She had been 25 pounds below her normal weight for several years, and she had many headaches, some of which occurred premenstrually.

On examination she appeared thin but quiet. The pulse was 98. There was no exophthalmos, but a fine tremor and a diffuse goiter were present. The basal metabolic rate before treatment was + 35 and + 42 per cent, with a pulse of 96, and weight average 108 pounds.

P. U. E. was given for one week after and Theelin for one week before succeeding menses. The metabolic rate dropped to + 23 per cent. P. U. E. was then given daily for five weeks during which a regular and an early menstrual period occurred. Toward the end of this course the metabolic rate rose sharply to + 45 per cent. No menses then occurred for five weeks and with the return of regular menses, as in Case 9, a distinct transition toward recovery took place. Weekly metabolic rate readings dropped rapidly in nine weeks to + 2 per cent, with a pulse of 68, and weight 116 pounds—a gain of 8 pounds. The last observation four months later is + 10 per cent, pulse 76, weight 111 pounds. The patient states that she is doing her usual amount of housework.

Summary

Thirteen cases of hyperthyroidism have been treated with pregnancy urine extract and Theelin (see table 1). The usual course of treatment

TABLE I

	Age	Apparent Ovarian Function	Average B.M.R. before Rx.	Duration of Treatment	B.M.R. after Rx.	Comment
Group I						
Case 1, Mrs. M.	53	Menopause	+30	3 months	+30	Postmenopause
Case 2, Mrs. S.	46	Regular	+38	5 months	+57	Goiter, 23 years. Hypertension
Case 3, Mr. E. A.	17	—	+43	5 months	+26	Male
Group II						
Case 4, Miss V. P.	19	Irregular	+15	½ month	− 3	B.M.R.—8% 18 months later
Case 5, Mrs. M.	33	Normal	+29	2 months	+ 4	
Case 6, Miss G. deF.	17	Normal	+50	1½ months	− 2	B.M.R.—4% 13 months later
Case 7, Mrs. A. W.	22	Normal	+49	5 months	+ 1	B.M.R.—10% 10 months later
Group III						
Case 8, Mrs. M. P.	34	Normal	+45	3 months	+55	Initial success, infection-failure
Case 9, Mrs. M. M.	30	Reduced	+40	1½ months	+54	Pelvic infection, ovariectomy
Case 10, Mrs. M. C.	25	Unknown	+50	3 months	+50	Atypical myasthenic hyperthyroidism
Group IV						
Case 11, Mrs. P. R.	41	Reduced	+57	7 months	+17	Amenorrhea has occurred
Case 12, Mrs. B.	38	Normal	+56	5 months	+15	Marked gain of weight and strength
Case 13, Mrs. L. T.	35	Normal	+38	5 months	+ 9	Normal activity

lasted for four or five months; the shortest was two weeks, the longest seven months. Remission of hyperthyroidism has occurred coincidental with this treatment in seven cases. The six failures are as follows: A boy; a woman two years past the menopause; a woman with hypertension and nodular goiter of 23 years' duration, who was at the menopause; a woman in whom remission had been induced, who experienced an upper respiratory infection; a woman of 34 years who had had two pelvic operations for infection and adhesions, in one of which the right ovary had been removed; and a negress with excessive, atypical myasthenic hyperthyroidism. The women in whom the treatment has been successful are definitely below the menopause; they have no history of ovarian disease. It would, therefore, seem that the induction of remission by pregnancy urine extract is dependent on normal ovarian function.

DISCUSSION

At the present time no physiological proof that the remission occurring in these cases may be attributed to the P. U. E., and Theelin treatment can be given because the mechanism of such an action is unknown. Nevertheless, remissions have occurred, abruptly in the healthiest adolescent girl,

TABLE II

Case 1—Total dosage	P. U. E. 45 c.c.		
	Theelin 45 c.c.		
Case 2— " "	P. U. E. 7 c.c.	}	in October
	Theelin 14 c.c.	}	
	P. U. E. 12 c.c.		in November
	P. U. E. 14 c.c.		in January
Case 3— " "	P. U. E. 60 c.c.		
Case 4— " "	P. U. E. 8 c.c.		
Case 5— " "	P. U. E. 24 c.c.		
Case 6— " "	P. U. E. 9 c.c.		
	Theelin 12 c.c.		
Case 7— " "	P. U. E. 4 c.c.		in February
	14 c.c.		in March
	8 c.c.		in April
	18 c.c.		in May and June
Case 8— " "	P. U. E. 8 c.c.		in February
	8 c.c.		in March
	10 c.c.		in May
	6 c.c.		in June
Case 9— " "	P. U. E. 15 c.c.		after menses
	Theelin 7 c.c.		before menses
	P. U. E. 6 c.c.		after menses
Case 10— " "	P. U. E. 33 c.c.		
	Theelin 26 c.c.		
Case 11— " "	Theelin 15 c.c.		
	P. U. E. 7 c.c.		following menses
	Theelin 9 c.c.		next 3 months
	P. U. E. 11 c.c.		" 3 "
Case 12— " "	P. U. E. 21 c.c.		daily
	P. U. E. 16 c.c.		alternately
	Theelin 21 c.c.		alternately
	P. U. E. 7 c.c.		after each menstrual period
Case 13— " "	P. U. E. 4 c.c.		after menses
	Theelin 4 c.c.		before menses
	P. U. E. 18 c.c.		daily.

and more gradually in the adult women. In two cases the return of menstruation, which had ceased during P. U. E. treatment, was coincident with remission as evidenced by gain of weight, previously stationary, and reduction of metabolic rate to or nearly to the normal zone.

In attempting to explain this remission one might be led to assume that a suppression of pituitary function had occurred as a result of P. U. E. administration. This would be beneficial if hyperthyroidism were due to excess of thyreotropic hormone from the anterior pituitary. This latter, an attractive hypothesis—hyperpituitary hyperthyroidism—while probable in some cases, has no evidence to support it. Indeed Aron [2] suggests just the opposite—that in hyperthyroidism, thyreotropic pituitary hormone production is reduced, while in hypothyroidism it is increased.

Largely as a result of the clinical observation that remission can not be produced in the absence of cyclic ovarian function, we are for the present using the working hypothesis that the pregnancy urine extract effect on hyperthyroidism is due to its action on the ovary. A small number of clinicians have reported the histologic change occurring in the human ovary after the administration of P. U. E. The work of Geist [3] and Mandelstamm [4] has previously been referred to. More recently Hamblen,[5] using

Antuitrin S, has also found not luteinization but on the contrary, in nearly every case, multiple follicular retention cysts. He suggests that folliculin production may be increased. Collip's [6] studies suggest that the universal effect of A. P. L. is not the formation of corpora lutea but an action on the theca interna. One might then suppose that the mechanism involved is as follows: A primary stimulation of Theelin secretion and circulation (as in Cases 4 and 6) or an early follicular retention of Theelin leading to delay or cessation (as in Cases 12 and 13) followed by a steady and heightened circulation of Theelin when administration of P. U. E. was discontinued. Riddle [7] has demonstrated in ring-doves that in spring and summer when ovarian weight and reproductive activity are increased, thyroid weight and activity are decreased, but that the thyroid is hyperplastic during the 44 hour ovulation period in the pigeon. Sherwood, Savage and Hall [8] found that daily injections of from 10 to 800 rat units of Amniotin lowered the metabolic rates of rabbits 37 per cent when these animals were also being given thyroid, and lowered the rates of rats 42 per cent below normal in oöphorectomized animals and 20 per cent below normal in intact animals. The effect of theelin on thyroid activity has been studied by Aron [9] who found that large doses of "folliculin" would prevent the thyroid hyperplasia of pituitary thyreotropic hormone. Kunde [10] found the metabolism of normal adult female dogs to be slightly lowered by continuous administration of estrin with production of estrus. More recently Laprida [11] produced regression of thyroid activity in the rat by injections of "folliculin." We, therefore, assume that immediate or delayed increased Theelin secretion and circulation result from the pregnancy urine extract injections and that this increased level of Theelin in the blood stream inhibits the thyroid. We realize that this theory is at present purely speculative.

Conclusion

Remission of hyperthyroidism occurred in seven young women treated with pregnancy urine extract (Antuitrin S and Theelin). This remission has now continued for 18 months in the earliest successful case. No recurrence in others has been observed as yet. It is assumed from our experience that this effect may be the result of an action of the extract on the ovarian production of Theelin. From our experience in six other cases such treatment would not be productive of remission in women at or beyond the menopause or in those in whom interference with ovarian function by surgery or disease has occurred.

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THE INCIDENCE OF STREPTOCOCCAL INFECTION IN CARDIOVASCULAR SCLEROSIS *

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There is a form of cardiovascular disease, seen more frequently than that due to syphilis, which is characterized by dilatation of the aorta and large vessels and a gross enlargement of the heart without special valvular defects. Its clinical course resembles that of syphilis in that symptoms referable to congestive failure make their appearance usually in the fourth and fifth decades of life. When aortic regurgitation is absent in cardiac syphilis a differential diagnosis between the two forms of heart disease may be quite impossible to make during life, and indeed at times a pathological anatomic differentiation may be impossible without the recognition of spirochetae in the tissues. This form of heart disease is usually referred to generically as degenerative cardiovascular disease, atherosclerosis, atheromatosis, chronic myocarditis, or simply the arteriosclerotic heart. Albrecht [1] (1906) referred to the associated dilatation of the aorta and large arteries as an idiopathic form of arteriosclerosis, and believed the mechanical factors of stress and strain, the local impinging of the blood stream upon the walls, to be the principal cause of it.

When congestive failure sets in, the clinical course of the patient suffering from this form of heart disease is, again like that of syphilis, as a rule, progressively down hill; a fair degree of recompensation, as seen with the rheumatic heart, does not follow treatment. The patient dies during his first period of failure or he lingers on, a complete invalid, for at most two or three years. Before the onset of failure, death frequently occurs from acute coronary occlusion or one of its sequelae, such as rupture of the heart wall. Sixty-five per cent of Benson and Hunter's [5] series of 200 cases of acute coronary occlusion belonged in this group of cardiopathies; the remaining 35 per cent were divided about equally between the syphilitic heart and the heart of senile arteriosclerosis. Likewise in their [6] series of 40 cases of rupture of the heart there was but one instance of proved syphilis, the remaining cases belonging to the group now under discussion.

It is agreed by all workers in the field of arteriosclerosis that the structural changes in the wall of this type of sclerotic artery are different from those of syphilis, from the medial lesions caused by adrenalin, and from those seen in the Mönckeberg type of the disease. There is no agreement, however, as to the nature of the cause or causes of the type of sclerosis under discussion. It would seem that several factors may be concerned. The

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mechanical factor of stress and strain, and the changes incident to disturbed metabolism—with high protein and high fat intakes leading to deposition of cholesterol esters in the intima—have been considered the most probable causes.[1, 2] But, seemingly, investigators will not give up the idea that infection in some way plays a rôle in the pathogenesis.[3] By experiments on rabbits and dogs, the results of which are certainly not applicable to man in their entirety, and by the statistical studies of clinical cases and necropsy material, an effort has been made repeatedly to link infection with the disease. Klotz (1912) from a study of the aortae and coronary arteries in 15 cases of acute rheumatism, states the arteries react to the irritant in a true inflammatory manner. In the small arteries a nonsuppurative infiltration chiefly of lymphoid cells is seen in the adventitia and outer layers of the media. In the larger vessels and the aorta the inflammation follows the vasovasorum. The intima does not seem to be primarily affected, but later proliferates. It is a picture of chronic productive mesoaortitis more like that of syphilis than true arteriosclerosis. Boinet and Romary (1897) found streptococci in early arteriosclerosis of the aorta in a patient dead of erysipelas and in another dying of rheumatic pericarditis. Ophül's very comprehensive study of necropsies from the standpoint of the relation of previous infections to the presence of arteriosclerosis found at autopsy led him to the conclusion that infections of the rheumatic type played an important rôle. He states that the arterial lesions seemed to reach their full development after the active infectious process had long subsided. In the seventh of the conclusions at the end of his monograph he says: "The tissue changes in arteriosclerosis are partly inflammatory but to an equal extent degenerative and reparative. In the arterioles the initial lesion seems to be a lateral subendothelial hyaline thrombosis followed by organization. In larger arteries there is evidence of endothelial damage, permitting the entrance into the intima of blood plasma and blood cells followed by proliferation and degeneration."

Although the experimental evidence of the relation of infection to arteriosclerosis is suggestive and the statistical studies of necropsy material point the finger of suspicion to the same, MacCallum [4] in a recent review of "Acute and Chronic Infections as Etiological Factors in Arteriosclerosis" concludes that: "In spite of these experiments and the statistical studies of coexisting or later occurring arteriosclerotic lesions in persons affected with infectious diseases, there is no satisfactory proof of the thesis that infection is the direct cause of arteriosclerosis." Again, he summarizes the subject matter in general as follows: It appears that there is but little evidence in favor of the idea that infections, whether acute or chronic, play a great part in the pathogenesis of arteriosclerosis. In typhoid fever the lipoid streaks may be a transitory phenomenon. In tuberculosis, rheumatism, arthritis, *Streptococcus viridans* endocarditis and septicemia, and in glomerular nephritis from infections, there is no special tendency to the development of arteriosclerosis. In diabetes mellitus, arteriosclerotic nephritis and cholelithiasis one finds arteriosclerosis in the majority of cases.

With this background of confusion in mind the clinician is occasionally brought face to face with instances of congestive heart failure which can not be relieved by the usual methods and principles of therapy. He is then undoubtedly justified in such instances in searching for and removing, if possible, any disease which may have some bearing upon the irrelievability of the condition in question. Actuated by these motives, we have collected in the past few years a small series of cases in which the cardiac conditions found present seemed to be related to the presence of chronic sinusitis, of chronic cholecystitis, and of severe grades of chronic pericemental dental infection. The coincidence of cholecystitis and heart disease has been noted several times by pathologists. Benson, Hunter and Manlove [6] found cholelithiasis present in 17.5 per cent of their 40 cases of heart rupture. In only one instance of this series was the rupture due to a proved syphilis. The possible relationship between gall-bladder disease and heart disease has also been commented upon by clinicians.[7] To us the group in which chronic hyperplastic sinusitis seemed to have some bearing has been of more interest, and we have studied the biopsy material and in one instance the heart removed at autopsy in the hope of finding suggestive evidence of an etiological relationship.

The following histories of some of the patients, briefly outlined, give the important clinical points in the series:

Case Reports

Case 1. R. M. W., a business man, aged 59, entered the hospital (*3/7/27*) with cardiac failure on the basis of chronic cardiovascular sclerosis with hypertension. Under hospital control it was found impossible to restore compensation by the usual principles of treatment. Orthodiagraphic measurements of the heart gave: aorta 5.6 cm., right heart 7.3 cm., left heart 12.5 cm., cardio-thoracic ratio 65.4. The palpable arteries were thickened 2+, on a basis of 1+ to 4+; the arch of the aorta was uniformly widened. He had badly diseased tonsils and a chronic hyperplastic disease of both antra. In the hope of obtaining compensation, it was decided to remove carefully all pus foci. June 1, tonsillectomy was performed and the patient had a stormy convalescence. The degree of his heart failure increased temporarily. On June 29, a double radical antrum operation was performed without much disturbance. Following the removal of the infected tissues, compensation returned promptly and quite satisfactorily. For a year and a half he was in sufficiently good health to return to his business. He then died suddenly from acute coronary occlusion. (Photomicrographs accompany the paper "Chronic Sinus Infection in Relation to Systemic Disease," Ann. Int. Med., 1931, iv, 752; Figures 12, 13, 14, 15, 16, 17.)

Case 2. (*6/8/29*) G. C., a man, aged 62, had suffered shortness of breath for six years; had been easily exhausted for the past four years, and worse the past month. He had had a chronic cough, nonproductive most of the time, and periodically a postnasal discharge. His blood pressure had been somewhat elevated for at least two years. Shortness of breath was the most distressing symptom. One flight of stairs had to be taken very slowly; and this exertion was accompanied by dyspnea and heart palpitation. For the past three years he had been considered primarily a cardiac case, and his life had been modified to meet this condition. Undoubted cardiac pathology existed. Electrocardiograms indicated a right bundle branch block. The palpable arteries were thickened 2+, on a basis of 1+ to 4+. The arch was

uniformly widened, but the right heart measured 3 cm. and the left heart 9.8 cm., and the cardio-thoracic ratio was within 50 per cent. The absence of substernal dullness pointed to the absence of definite congestive failure. Because of the absence of such failure, the possibility of chronic sepsis being the primary cause of his illness was considered. As he suffered from a pansinusitis, a double radical antrum operation, and a trans-antral ethmosphenoidectomy on both sides were performed. There was definite hyperplasia of all the lining membranes without free pus. Symptomatic recovery was prompt. Four months after operation he reported feeling well. He had no dyspnea, and no other subjective symptoms of heart trouble. His blood pressure was 144 systolic and 76 diastolic. Three months later he again made the same report. At the present time (1934) he is still well. He is a lawyer by profession and works daily. (This case is not included in table 1 because the sinus tissues were not stained for bacteria.)

Case 3. (5/30/32) G. D. R., a business man, aged 56, was awakened at night on April 30, 1932 with acute dyspnea, which was relieved by sitting up. He experienced no pain but there was a definite sense of anxiety which left as soon as his breathing became quiet. There was no coughing or wheezing, no frothy or bloody expectoration. Shortness of breath had continued until the present time. All palpable arteries were thickened 3+, on a basis of 1+ to 4+. The arch of the aorta was sclerotic, measured 5.2 cm. and was uniformly widened. The right heart measured 5.3 cm., the left heart, 8.5 cm., and the cardio-thoracic ratio was 47. The blood pressure was 92 systolic and 74 diastolic. Negative T-waves were noted in both Leads I and II. Occasional left ventricular premature beats were present. A hyperplastic sinusitis existed in both antra with a large filling defect in the right. Radical exenteration of both antra, together with a transantral ethmoidectomy, was done June 9, 1932. Complete relief from the cardiac symptoms has thus far been obtained.

Case 4. (11/22/32) G. T. K., a farmer, aged 59, had had congestive heart failure for five months, becoming progressively worse. The heart measured: aorta 6.1 cm., right heart 6 cm., left heart 10.8 cm., with a cardio-thoracic ratio of 53.6. The arch was uniformly widened, sclerotic, and contained calcareous plaques. The blood pressure was 170 systolic and 90 diastolic. The palpable arteries were thickened 2+ and 3+, on a basis of 1+ to 4+. There were negative T-waves noted in Lead I, slight splintering of the S, particularly in Lead II, and T's of high amplitude in both Leads I and III. Chronic hyperplastic antrum infection existed with cyst formation in the right. It was found impossible to recompensate his heart, and, in view of this fact, radical exenteration of the sinus infection was performed. Following the operation, recompensation was obtained. During a short period of time auricular fibrillation set in, but this was broken back to a sinus rhythm with 6 grains of quinidine sulphate. During convalescence a left cerebral thrombosis of minor grade appeared, which affected the speech and the right side of the body for several days, after which time the symptoms disappeared. The patient got up and about and returned to his home. His heart again went into failure in the late summer of 1933 and he died from this cause.

Case 5. (2/1/33) G. F., a farmer, aged 66, entered the hospital with congestive failure on the basis of cardiovascular sclerosis with auricular fibrillation. He had been short of breath for three or four years. One year ago he stopped all work and has been in bed much of the time. He had severe dental sepsis and hyperplastic double antrum disease. The arch of the aorta was uniformly dilated. It measured 5.7 cm., the right heart 5.7 cm., the left heart 15.3 cm., and the cardio-thoracic ratio was over 64. The palpable arteries were thickened 3+, on a basis of 1+ to 4+. The blood pressure was 170 systolic and 120 diastolic. All teeth were removed. On March 1 radical exenteration of both antra was performed, a very pronounced

TABLE I

Sinus Tissues Examined for the Presence of Microörganisms in the Walls of Blood Vessels

Number	Sex	Age	Diagnosis in addition to sinus disease	Sclerosis of vessels in sinus tissues 1+ to 4+	Diplococci in vessel walls	End results
Symptoms Due to Cardiovascular Disease						
1	M.	59	Atheroscler. 4+ failure	4+	Positive	Improved. Died 2 years later of coronary thrombosis.
3	M.	56	Atheroscler. 3+	4+	"	Good.
4	M.	59	Atheroscler. 4+ failure	4+	"	Improved. Died one year later of congestive heart failure.
5	M.	66	Atheroscler. 4+ failure	4+	"	Improved. One recurrence of failure and recompensated.
7	M.	63	Atheroscler. 4+ failure Toxic nodular goiter previously removed	4+	"	Improved. Died 2 years later of congestive heart failure.
6	M.	56	Atheroscler. 3+ angina	—	—	Coronary arteries 4+. Diplococci + in walls. Died 2 years later of coronary thrombosis.
Symptoms Not Due to Cardiovascular Disease						
7	M.	60	Atheroscler. 1+	2+ Patchy	"	Good.
8	M.	41	Rheum. endocard. Atheroscler. 1+	2+	"	Improved.
9	F.	40	Asthma Nodular goiter Atheroscler. 2+	2+	"	Good.
10	F.	39	Rheum. endocard. Atheroscler. 1+	3+	"	Improved.
11	M.	61	Alcoholism Atheroscler. 2+	2+	"	Not improved.
12	M.	69	Cholecystitis Prostatism Atheroscler. 2+	2+	"	Died later. Ca. stomach.
13	F.	60	Cholecystitis Atheroscler. 2+	3+	"	Improved.
Microörganisms Not Found in Vessel Walls						
14	F.	65	Spinal arthritis Thyroid heart Mild failure Aur. fibrillation Atheroscler. 2+	2+	Negative	Good.
15	M.	49	Arthritis Arteries 1+	1+ to 3+ Patchy	"	Good.
16	M.	64	Neuritis Aorta 2+	1+	"	Died later of myeloid leukemia.
17	M.	55	Asthma Atheroscler. 2+	1+		Died during attack of asthma. Autopsy showed cardiovascular sclerosis of moderate grade.
18	F.	64	Arthritis Aorta 2+ Radials 1+	2+	"	Good.

pyogenic membrane being found particularly on the left side. The heart became recompensated and the patient returned home to remain fairly well through the summer. In October he returned once more in mild failure, and was recompensated. (Figures 1 and 2.)

Case 6. (3/17/30) J. W. C., a business man, aged 56, had suffered for some years with symptoms of pressure about his heart, associated with the belching of gas and

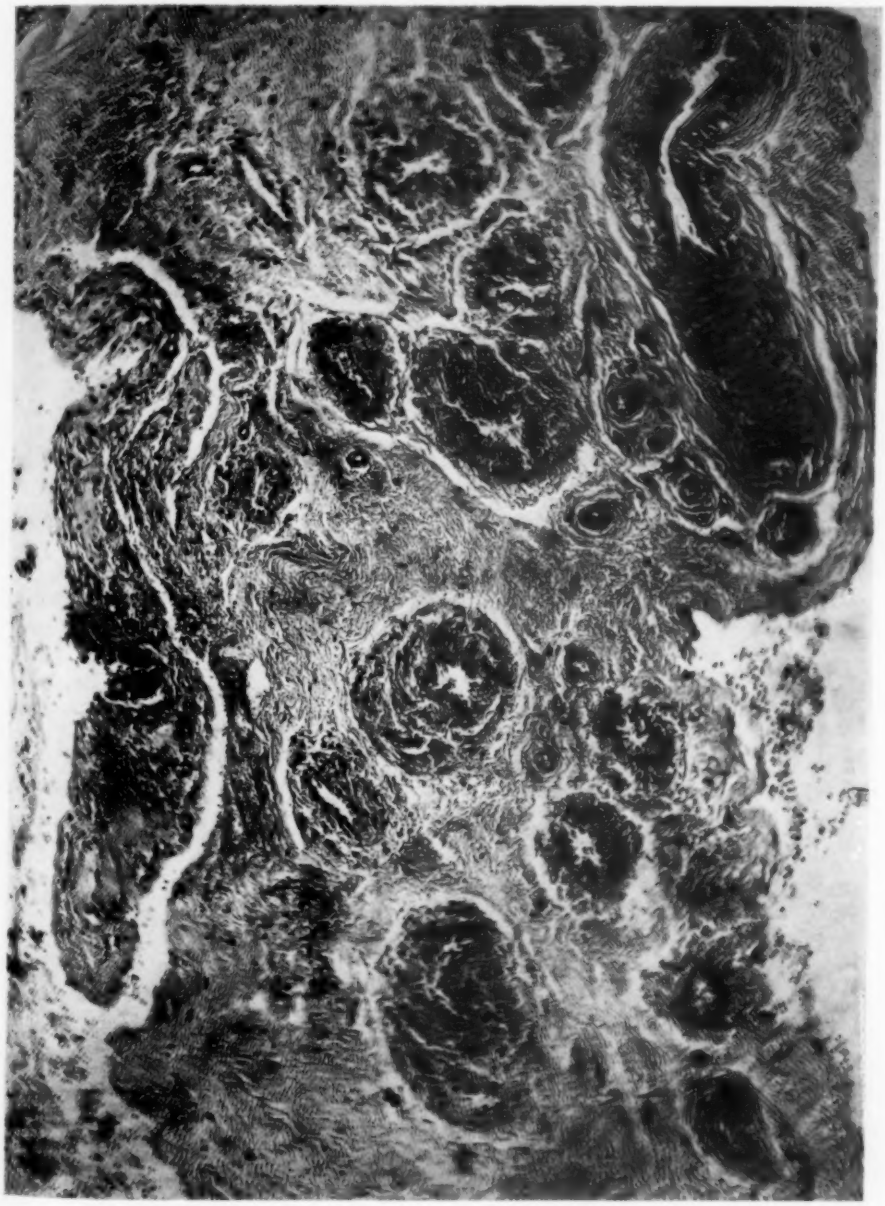

FIG. 1. (*Case 5.*) Sinus membrane. Fibrosis of the walls of the small arterioles. × 180.

some constipation. He had suffered no symptoms of cardiac failure. His heart measurements were: aorta 5 cm., right heart 4.2 cm., left heart 10.6 cm., with a cardiothoracic ratio of 46.6. The arch was moderately widened and the palpable arteries were thickened 2+, on a basis of 1+ to 4+. Blood pressure was 186 systolic and 122 diastolic. He had a well marked hyperplastic inflammation of both antra. Radi-

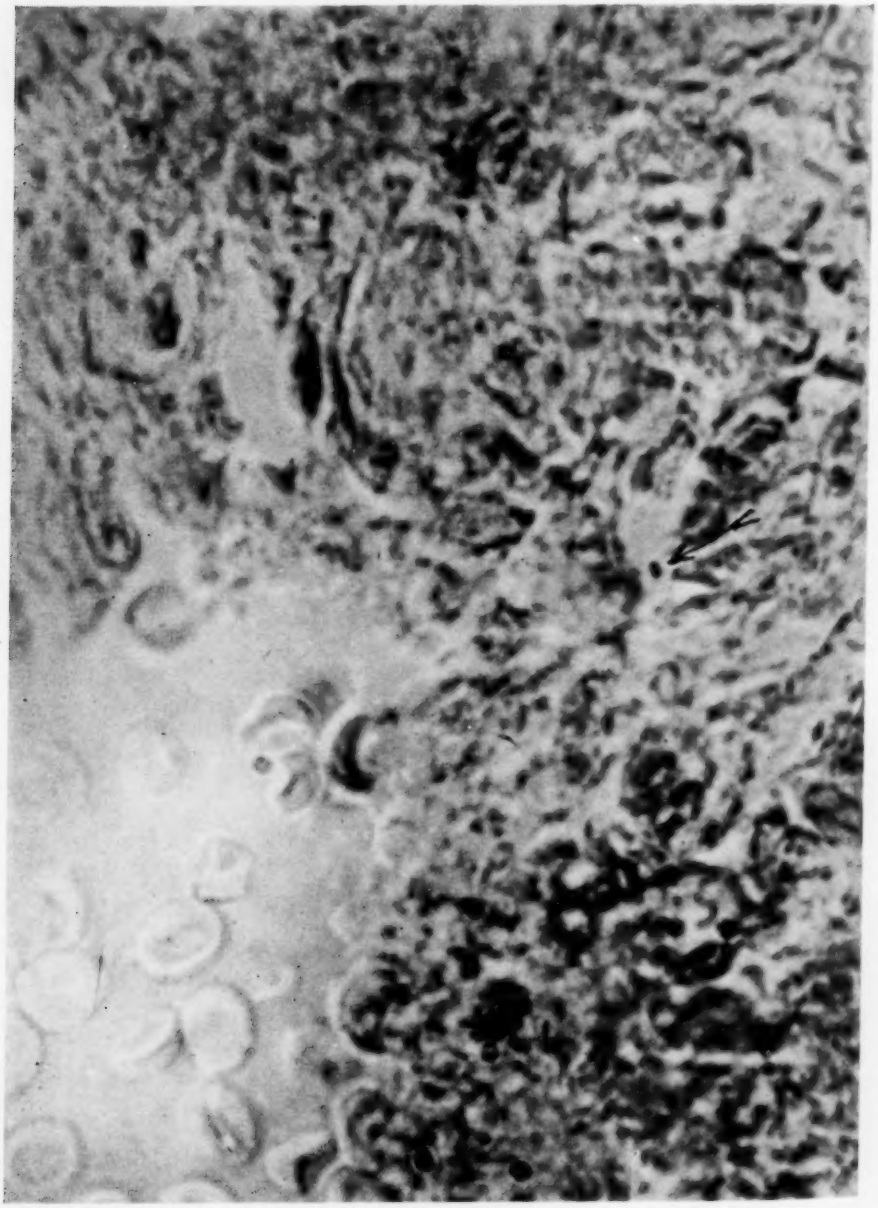

FIG. 2. (*Case 5.*) Sinus membrane. Diplococci in the walls of a small arteriole, the seat of fibrosis. × 1900.

cal exenteration was advised but not accepted. In April 1932, he died suddenly from an acute coronary occlusion. (Figures 3 and 4.)

Tissues from the sinuses not only from these cases of frank heart disease but also from a number of patients suffering from other ailments have been studied with reference to the structural changes in the blood vessels of

FIG. 3. (*Case 6.*) Section of branch of coronary artery. Fibrosis and narrowing of the lumen. × 30.

the membranes and the presence of microörganisms within their vessel walls. Data from all of the cases are given in table 1. These data reveal a rough parallelism, in the limited number of cases examined, between the finding of bacteria in the tissues and the degree of sclerotic changes present.

Microscopic Structure of Arterioles in Diseased Sinus Membranes. A

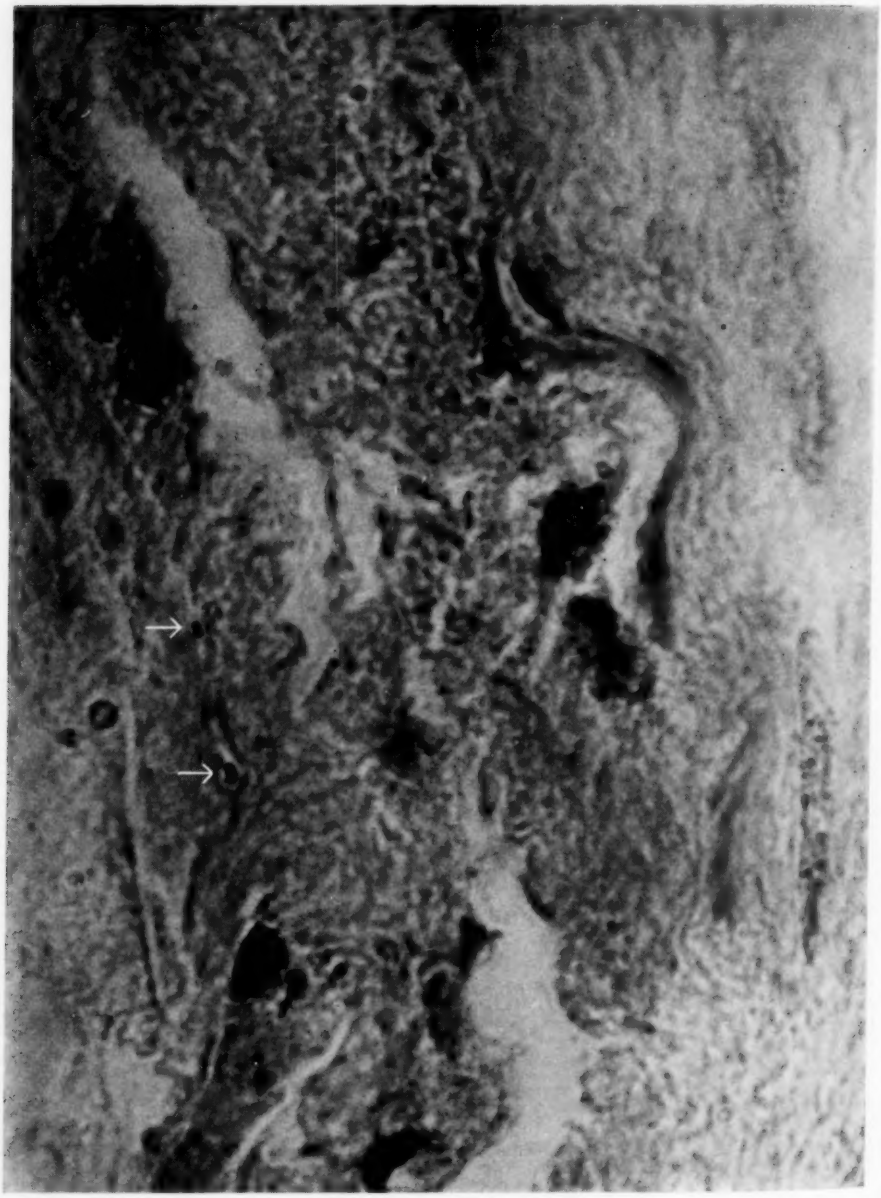

FIG. 4. (*Case 6.*) Diplococci in the wall of coronary vessel. × 1900.

study of the histological changes in the structure of the blood vessels in sinus membranes, the seat of chronic infection, and a search for microorganisms in the walls of the vessels have been made in 18 cases.* The structural changes noted have been quite similar in all the vessels, but vary in degree. Hyaline degeneration and swelling, especially subintimal, narrows the lumen and oftentimes completely closes it. There is a diffuse proliferative fibrous tissue widening of the adventitia and media and at times the entire wall of the smaller vessels is involved in this manner. Here and there a diffuse inflammatory process with coarse fibrin deposits is noted. At times apparent edema of the media exists. There are frequently seen many polymorphonuclear leukocytes in the zone between the intima and the media. Small round cells and plasma cells occur in some areas but histiocytes are as a rule few in number. In Case 7 there are, however, numerous histiocytes, small round cells and a few eosinophiles around and in the walls of many of the vessels.

Bacterial stains reveal numerous microörganisms in the sinus membranes. Many of these organisms are found in the walls of the small arterioles, both in the subintimal proliferations of fibrous connective tissue and in the outer media and adventitia. These organisms are all in the form of small diplococci which have the morphology and staining reactions of streptococci. They are frequently found close to the collections of small lymphocytes and plasma cells in the tissues of the blood vessel walls.

The microscopic structure is that of a diffuse subacute arteritis.

Microscopic Structure of Coronary Arteries in Case 6 (Figures 3 and 4). Tissue blocks, taken from the heart shortly after the death of this patient, were kindly sent to us by Dr. G. F. Strong of Vancouver, B. C. Gross

* Tissue stains used were:
1. Giemsa stain—standard technic.
2. Maximow's hematoxylin, azure eosin.
3. Azin carmine.
4. Hematoxylin and eosin.

Technic of Staining for Gram Positive Bacteria in Tissues. All tissues were immediately fixed in Formo-Zenker's solution upon removal in the surgery, and were later embedded in paraffin. Sections were cut 5 micra thick. They were treated with xylol, alcohol, water, Lugol's solution, sodium thiosulphate and water. After the water, the sections were stained for 2 minutes with ammonium oxalate crystal violet, washed in water, destained in 80 per cent alcohol until a very pale blue; run through alcohol, xylol and mounted in balsam.

Bacteria show a deep purple color against an almost colorless tissue background.

Crystal violet formula:

Crystal violet	2.0 gm.
Alcohol 95%	20.0 c.c.
Amm. oxalate 1%	90.0 c.c.

Dissolve and filter

Formo-Zenker solution:

Formalin 40%	5 c.c.
Zenker's sol.	95 c.c.

Lugol's solution: $I : KI : H_2O :: 1 : 2 : 100$.

The proper staining of bacteria in tissues is attended with much difficulty. This is the reason for detailing the technic used. Dr. E. C. Rosenow, Mayo Foundation, first taught us a satisfactory method after over a year had been spent with indifferent results. Later A. L. R. perfected the above technic which gives uniformly well stained preparations.

We would also here acknowledge our indebtedness to Dr. Frank R. Menne, Head of the Department of Pathology, for his assistance and criticism.

examination of the heart revealed the following: "The heart was examined without removing it from the body. It is but slightly enlarged. The aorta is of normal width and appearance throughout. The valves are all intact, although there is considerable sclerotic thickening in the aortic cusp of the mitral valve. The coronary arteries are markedly narrowed

FIG. 5. (*Case 9.*) Coronary artery from case recorded in table 2. × 300.

and sclerotic. Approximately 1 inch from the orifices of both right and left coronaries, the vessels appear almost completely occluded, admitting barely the point of a pin. About 1 inch from the orifice of the circumflex branch of the left coronary there is a fresh organized thrombus, which completely occludes the lumen. It is about 1 cm. in length, quite firmly ad-

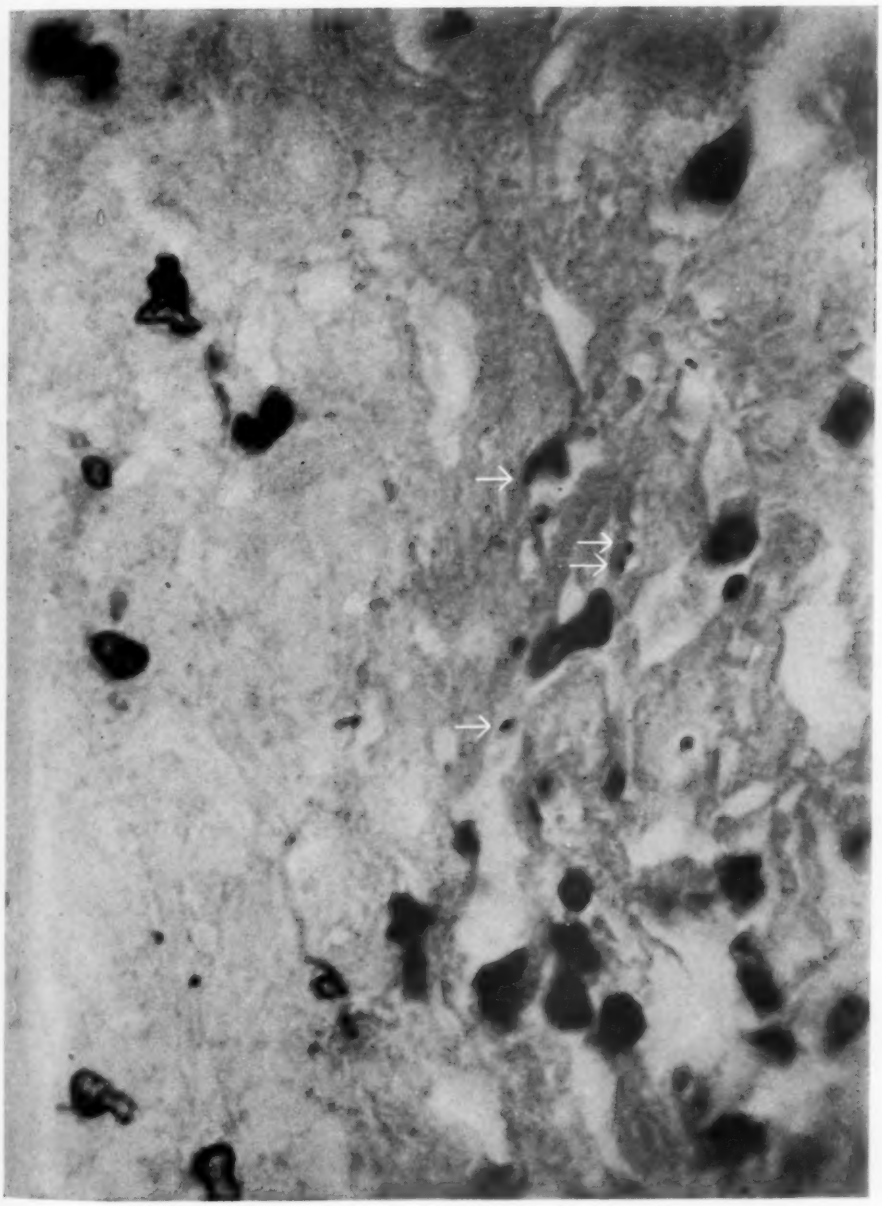

FIG. 6. (*Case 9.*) Coronary artery. Diplococci in fibrosed vessel wall. × 1800.

herent to the walls and to the site of an atheromatous plaque. The heart muscle is of fairly good consistency."

The lumen of the artery shown in figure 3 is markedly narrowed and slit-like. This is caused by a thickening of the wall due to a subintimal proliferation of fibrous connective tissue. In this area there are numerous

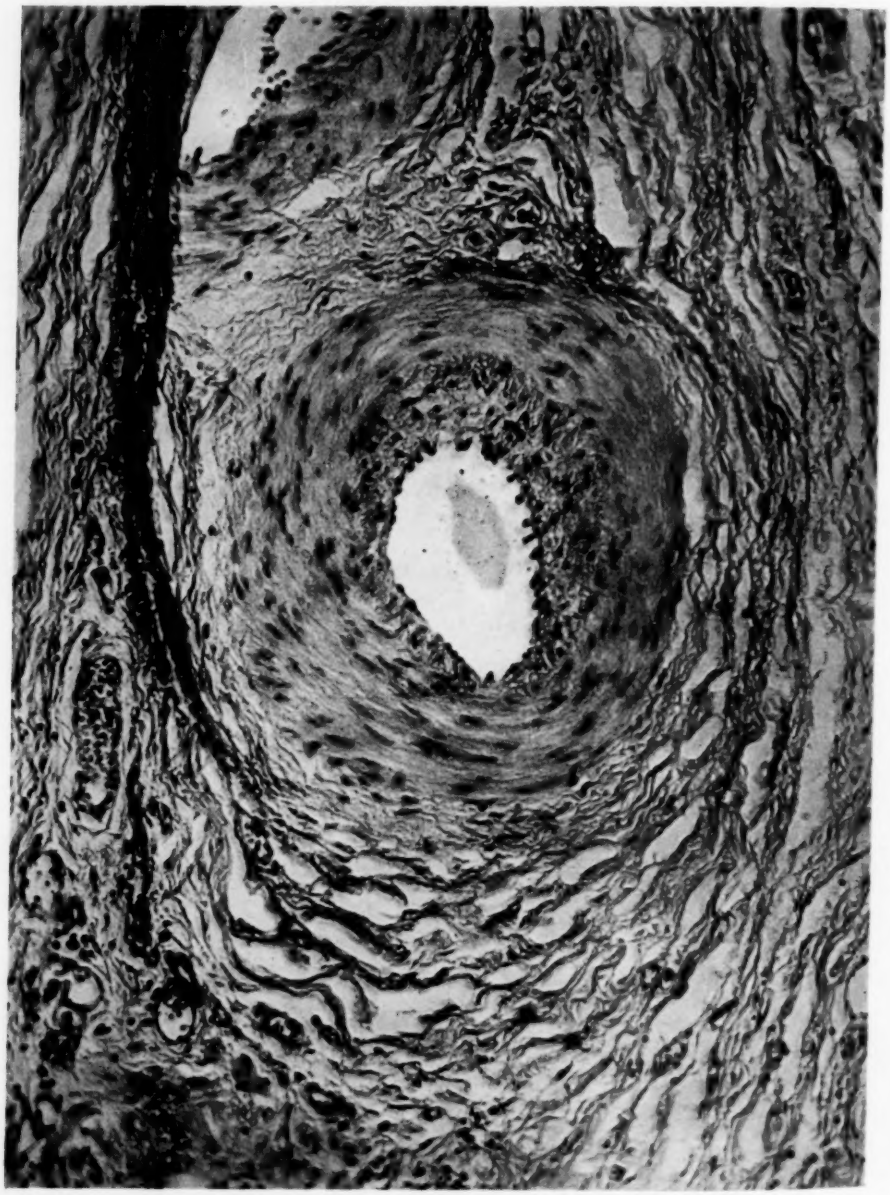

FIG. 7. No. S–96–34. Small arteriole within muscular layer of gall-bladder from a case of subacute cholecystitis. Arteriole shows fibrosis of its wall. × 300.

collections of small lymphocytes and plasma cells as well as cholesterol crystals. There is some edema in the areas where the chronic inflammatory cells are in greatest numbers. The outer media and inner adventitia are also involved by a fibrous connective tissue proliferation. Here there are likewise collections of small lymphocytes around the outer adventitia. Here are also a few dense collections of chronic inflammatory cells. Some of the small arterioles in the adventitia have markedly narrowed lumens due to the same proliferative process. Numerous diplococci are visible in specially stained sections. They are found to be most numerous around and in the dense collections of lymphocytes. These microörganisms have the same morphological and staining characteristics as those found in the sinus tissues and those seen in tissues taken from patients dying of streptococcic septicemia.

The microscopic structure is that of subacute arteritis with atheromatous degeneration.

Microscopic Structure of Coronary Arteries from Autopsy Material Taken from Patients Dying from Acute Coronary Thrombosis (Figures 5 and 6). For comparison with the microscopic picture seen in the coronary arteries in Case 6, we examined the material obtained at postmortem from 11 unselected patients dying from acute coronary thrombosis. (Table 2.)

In all sections there is some degree of atheromatous degeneration, but in no instance is this process advanced enough to cause marked narrowing of the vessel lumens. The lumens of the vessels are filled by fresh thrombi in all cases except one (3). In this case organization with recanalization has taken place. The fresh thrombi are adherent to the endothelial lining of the vessels and are formed by intact blood cells in a matrix of fibrin and platelets. The intima is greatly thickened due to proliferation of fibrous connective tissue. The media and adventitia are thin. In this subintimal proliferation and also in the outer media and adventitia there are varying numbers of small lymphocytes and plasma cells. In some places these chronic inflammatory cells are clustered close together and in other places are widely scattered. In a few instances, where larger arterioles were found, there is seen a marked subintimal proliferation causing narrowing of the lumen, and, in the adventitial area, collections of small lymphocytes. Bacterial stains of these tissues reveal varying numbers of diplococci and in a few instances single and short chain cocci. These organisms are found in the subintimal proliferative areas and in the outer media and adventitia. In some sections they are visible in the adventitia of the walls of the arterioles. The organisms are found for the most part in close relation to the denser collections of small lymphocytes.

The microscopic structure, again as in Case 6, is that of subacute arteritis, with atheromatous degeneration.

In the 11 cases chronic cholecystitis was present three times and a severe grade of pericemental infection and chronic sinus disease each twice.

TABLE II

Coronary Arteries from Acute Cases of Coronary Occlusion Showing the Incidence of Bacteria in the Vessel Wall

Case Number	Age	Sex	Branch of Coronary Artery	Sclerosis Basis 1+ to 4+	Histology of Intima	Histology of Media	Histology of Adventitia	Character of Thrombus	Thickness of Vessel Wall	Edema of Wall	Infiltration		Microörganisms			Other Pathology Found at Autopsy
											Amount	Type	In Wall	In Thrombus	Type	
1	70	M.	Left	2+ (hyaline)	Infiltrated; very thick; fibrous-hyaline	Thick; fibrous	Thick; hyaline	Fresh formed	0.5–1.0 mm.	0	3+	S. lymphocytes plasma cells	2+	0	Diplococci	Cholecystitis with cholelithiasis.
2	65	M.	Left	2+ (calcified)	Infiltrated; thick fibrous; atheromatous deg.	Thin	Thin	Fresh formed	1.0 mm.	0	2+	S. lymphocytes	2+	0	Diplococci	Chronic cholecystitis. Chronic fibrous appendicitis. Arteriosclerotic kidneys.
3	50	F.	Left	2+	Infiltrated; slight atherom. degeneration	Thin; degenerated	Thin	Recanalized thrombus	2.0 mm.	2+	1+	S. lymphocytes	2+	2+	Diplococci	Chronic cholecystitis. Chronic pleuritis.
4	55	M.	Right	2+	Infiltrated; thick; atheromatous deg.	Thin; infiltrated	Thin	Fresh	2–3.0 mm.	1+	3+	S. lymphocytes	2+	0	Diplococci	Pyorrhea and chronic antral infection. Purulent bronchitis.
5	60	M.	Left	2+ (calcified)	Thick; infiltrated; atheromatous deg.	Thin	Thin	Fresh	0.5–2.0 mm.	1+	2+	S. lymphocytes plasma cells	3+	2+	Diplococci Short chain cocci	Many carious teeth.
6	43	M.	Right	2+ (calcified)	Thick; hyaline-fibrous; atheromatous deg.	Thin	Thin	Fresh	2.0 mm.	0	1+	S. lymphocytes	2+	0	Single and diplococci	Chronic pleuritis. Mucopurulent bronchitis. Clinically nasal congestion. Asthma—septum resection.
7	60	F.	Left	3+ (calcified)	Thick; hyaline; not infiltrated; atheromatous deg.	Very thin	Very thin	Fresh	0.5–1.0 mm.	0	0	0	1+	0	Diplococci	Arteriosclerotic kidney. Chronic hyperplastic endometritis.
8	87	M.	Left	2+ (calcified)	Infiltrated; thick calcified; atheromatous deg.	Thin	Thin	Fresh	2–3 mm.	1+	1+	S. lymphocytes	1+	0	Single and diplococci	Sero-fibrinous pleuritis with effusion. Senile arteriosclerosis.
9	55	M.	Left	2+	Infiltrated; thick hyaline; fibrous	Thin	Thin	Fresh	1.0 mm.	0	2+	S. lymphocytes	1+	0	Diplococci	Healed duodenal ulcer.
10	60	M.	Right	2+	Infiltrated; very thick; atheromatous deg.	Thin	Thin; fibrous	Fresh	2.0 mm.	0	1+	S. lymphocytes	2+	0	Diplococci	Fibrinous pleuritis. Fibrinous pericarditis.
11	55	M.	Left	1+	Infiltrated; atheromatous deg.	Infiltrated; thin	Infiltrated; thin	Fresh	2–3.0 mm.	0	3+	S. lymphocytes	2+	0	Diplococci	Fibrous pleuritis. Arteriosclerotic kidneys.

Microscopic Structure of Arterioles in the Wall of the Gall-Bladder, the Seat of Subacute Cholecystitis (*Figures 7 and 8*). Because of the apparent clinical relationship occasionally seen between diseases of the gall-bladder and frank heart disease we studied the arterioles found in the smooth muscle layer of the gall-bladder in 12 cases of subacute cholecystitis. All of the

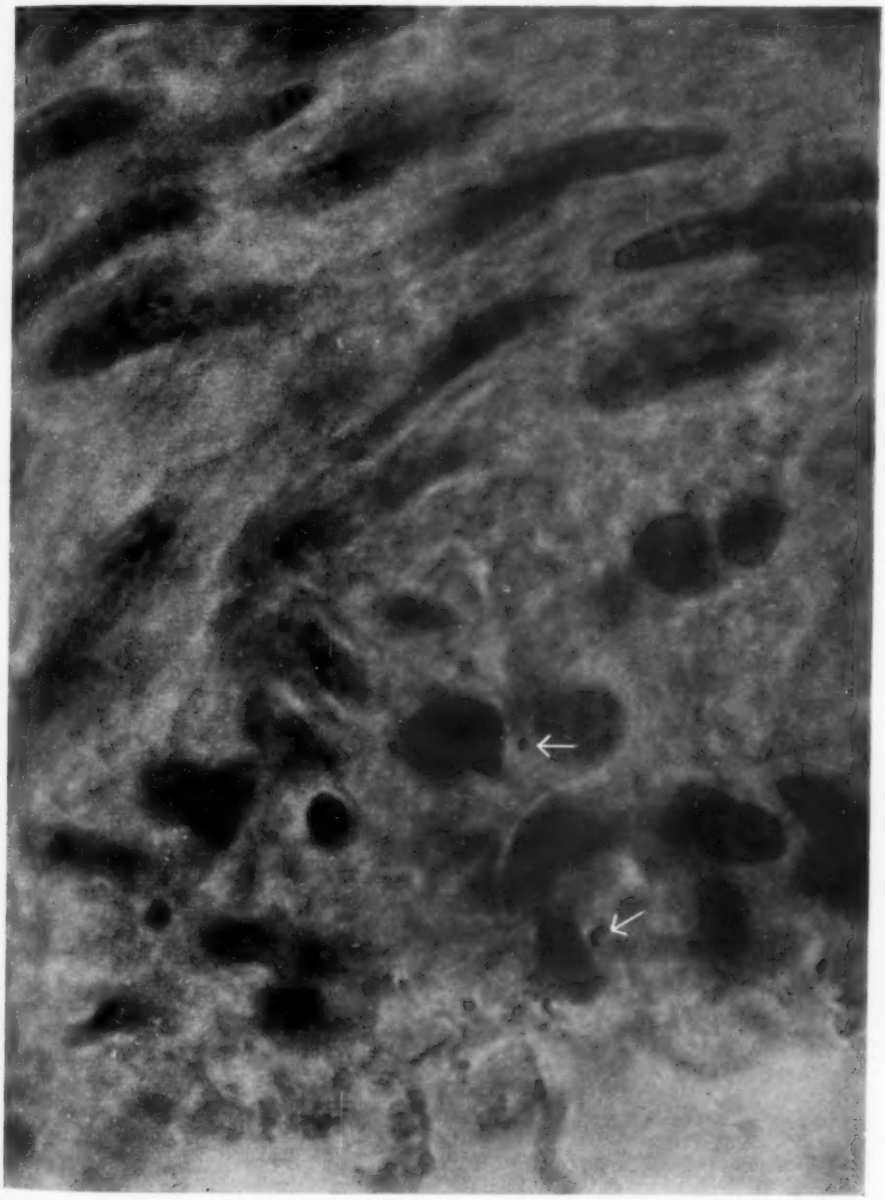

FIG. 8. No. S–96–34. Gall-bladder. Diplococci in walls of arteriole, the seat of subacute arteriolitis.

gall-bladders were removed at operation and placed immediately in Formo-Zenker's fluid. The clinical history of the following case is illustrative of the type of heart disease we have in mind.

A housewife (11047) 49 years of age, entered the hospital in February 1926 in severe congestive failure on the basis of a chronic hypertensive cardiovascular sclerosis with auricular fibrillation. She had first become breathless two years before, since which time she had not been well, and definite congestive failure had existed since August 1925. During most of this time she had been in bed. She had had attacks of gall-stone colic in 1915 and 1920. Following the first attack of colic the gall-bladder had been removed. Recompensation of the heart under control was not obtained, and during this period of treatment the patient suffered an attack of right upper quadrant abdominal pain with fever and slight jaundice, indicating the presence of common duct obstruction. She was operated upon in the presence of the heart failure and a common duct drainage instituted. Following the operation the heart became quickly recompensated and at the present time (1934) the patient is still living. In 1927 she went through a severe bronchopneumonia without again decompensating the heart. For a time the fibrillation was removed by quinidine sulphate but for the past two years it has been refractory to such treatment. At the time of first measuring the size of the heart, the orthodiagraphic measurements were: aorta 6.3 cm., right heart 5.9 cm., left heart 10.7 cm., cardio-thoracic ratio 57.0. One year later the measurements were: aorta 6.3 cm., right heart 5.7 cm., left heart 8.4 cm.

The small arterioles of the gall-bladders examined (figures 7 and 8) all present a subintimal fibrous connective tissue proliferative process which has caused a marked narrowing of the vessel lumen. Numerous small lymphocytes are found in the subintimal area. The outer media and adventitia are increased in width due to a fibrous connective tissue proliferation. Numerous diplococci are found in these proliferative areas. These microorganisms have the same morphological and staining characteristics as those found in the sinus membranes and coronary arteries. The microscopic structure, again, is that of a subacute arteritis, often obliterative.

In order to compare the blood vessel changes in the presence of chronic pus infection in other more distant tissues, examination of sections from a papilloma taken from the urinary bladder, the seat of a chronic inflammatory process, and sections from chronic cutaneous ulcers, caused by pyogenic microörganisms, were made. All of the small arterioles in the sections studied have thickened walls which have caused a marked narrowing of the lumens. The widening of the wall is due to a subintimal fibrous connective tissue proliferation. The media and inner portion of the adventitia are likewise involved by the same process. There are numerous small lymphocytes and a few plasma cells scattered throughout the vessel walls and diplococci are likewise present. The process is a subacute arteritis.

Comment

It is unnecessary to review in further detail the structural changes found in the blood vessels of the sinus membranes, the hearts, the gall-bladders, and the two other tissues presented in the text. These changes are seemingly

comparable to those described in experimental animals by a number of investigators. Especially interesting are the experimental lesions of the aorta and other arteries produced in rabbits by Benson, Smith and Semenov [8] by the repeated intravenous injection of streptococci over a long period of time. A comparison of their photomicrographs of the more chronic lesions with our own shows a striking similarity. We have not attempted to read into our findings the rôle of chronic infection as the primary factor in the causation of arteriosclerosis. We have discussed a small group of patients with congestive heart failure on the basis of chronic cardiovascular sclerosis in whom recompensation could not be obtained until after the removal of a coexisting chronic sinus disease. The character of the arterial lesions is described and the fact is stressed that diplococci having the morphological and staining characteristics of streptococci are present in considerable numbers in the arterial walls. The method of removal and fixation of the sinus membranes removes the criticism of possible postmortem invasion of these microörganisms. We have, moreover, considered these microörganisms to be streptococci because we, and our associates,[8] have cultured more than 400 sinus membranes from cases of chronic paranasal sinus disease and have found the predominating microörganisms to be streptococci. They were present in 94.5 per cent of the sinus membranes cultured; 35 per cent were identified as *beta*-hemolytic streptococci, 33 per cent as *alpha*-hemolytic green producing streptococci, 14 per cent as *Streptococcus viridans,* and 18 per cent as non-hemolytic streptococci of the *gamma* type. Other microorganisms occurred in combination with the streptococci but with minor frequency. One cannot, likewise, very well consider the mechanical factor of stress and strain to be of importance in the small arterioles of such tissues. Chronic hypertension was not present in all of the patients. One, Case 3, had a persistently low blood pressure, 92 millimeters of mercury systolic and 74 diastolic. As regards the influence of cholesterol we found cholesterol deposition in the walls of many vessels but it seemed to be less prominent than the inflammatory changes present. It is generally assumed now that heavy cholesterol feeding over a sufficiently long period of time will produce arteriosclerosis in rabbits. The work of a number of investigators would tend to show this. Benson and his co-workers were unable to produce arteriosclerosis in their rabbits by cholesterol feeding alone but when such feedings were given together with repeated induced infections, the changes in the arteries were much more marked than those due to infection alone. The thought behind our work has been that if chronic pus infections can be reasonably shown to have some relationship to the cause of this form of so-called degenerative heart disease, then the early prophylactic removal of such infections may lessen the number of coronary heart deaths now seen so frequently in the middle decades of life.

Summary

We have presented a small group of patients showing congestive heart failure on the basis of a chronic cardiovascular sclerosis, in whom recompensation could not be obtained until after the removal of a coexisting chronic sinus disease. We have described lesions in the arterioles of the sinus membranes removed by operation in these patients and have referred to them as being comparable with the arterial changes found in the heart and some other organs in both human and experimental animal material. The fact that microörganisms having the morphological and staining characteristics of streptococci were constantly found in comparatively large numbers within the walls of the arteries in all the tissues studied has been emphasized as suggesting a possible etiologic relationship.

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AN EXPLANATION OF THE MECHANISM OF INFANTILE PARALYSIS PRODUCTION IN THE HUMAN BEING*

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PART I

FABER [1] believed that a good theory for the explanation of the virus spread in poliomyelitis in man would be to assume that, after the virus entered the system along the olfactory terminal fibers, it spread by way of the olfactory tracts, through the hypothalamus, to the medulla, thalamus and midbrain, and then down the spinothalamic tract to the posterior column, finally reaching the anterior horn cell area in the cord. However, the possibility of extension by other pathways was not denied. His hypothesis was based upon clinical findings and upon evidence that was obtained from experiments on monkeys that had contracted the disease following intranasal instillation of poliomyelitis virus.

In the majority of human beings and monkeys, paralysis first develops in the muscles that receive their nerve supply from the lumbar enlargement and only secondarily in those whose nerve supply comes from the cervical area. This fact forms the basis for a fundamental objection to Faber's theory of virus spread, since it would be difficult to understand why the virus would travel down the spinothalamic tract in the cord, skip the cervical enlargement, and in most instances involve first the lumbar enlargement and paralyze first the muscles of the legs.

The spinothalamic tract carries pain and temperature sensations in the lateral column and touch and pressure in the ventral branch. The ventral fibers are not involved in this disease, since touch and pressure seem to be normal. As both fiber tracts run together in the spinal lemniscus, an almost anatomical predilection for the lateral tract would have to be presupposed to explain the absence of involvement of the ventral fibers, unless some other logical reason presented itself.

It is claimed that the hyperesthesia that appears sometimes before somatic paralysis suggests a prior localization of the disease in the spinothalamic tract. When I analyzed our cases I found that 63, or 14 per cent had hyperesthesia or pain; in 58 of these cases, the hyperesthesia occurred in response to deep pressure only and was usually limited to those muscles and tendons of muscles that later became paralyzed. The hyperesthesia was in the muscles and about the tendon ends and not in the skin. Stimulating the skin by stroking it lightly would only occasionally elicit pain (five cases). In other words, although the muscle tendons were painfully

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hyperesthetic on manipulation, the skin areas that had their nerve supply from the same segments were not hyperesthetic. This dissociation of light from deep sensibility may be the result of conditions other than the involvement of the spinothalamic tract per se.

Pain was occasionally present when pressure was applied over the vertebrae or when they were gently pounded; this was usually the case in the absence of any skin hyperesthesia.

The appreciation of temperature has always been normal in our clinical experience, although the skin of the leg or arm that is paralyzed may be colder than that of the non-paralyzed member. This, however, is an objective finding and may be totally unassociated with any central sensory lesion of the cord and may be easily explained on the basis of vasomotor phenomena secondary to a nerve irritation such as is seen in other types of paralyses. Though the skins of our patients were colder than is normally the case, all of those who were able to coöperate could easily tell the difference between heat and cold, an unlikely finding if the lateral spinothalamic tract were consistently involved. I do not think that Müller's observations on temperature dissociation would be agreed to by other clinicians.

The fact that no plausible reason is given as to why the disease is localized in the lumbar area and the fact that there is no good explanation as to why the mesenteric glands are sometimes enlarged cast some doubt also on Faber's theory of virus spread in the human, although one cannot deny that it may thus spread after the virus has been intranasally instilled.

Ataxia is mentioned in Faber's monograph. None of our patients ever had acro- or proximo-ataxia, since they always appreciated their position in space. Only occasionally, some of our patients seemingly had asynergy of movements somewhat athetoid in type, and even fibrillary twitchings have been seen; these might well have been clonic or tonic spasms, the causation of which might have been something totally remote from a lesion of the lateral spinothalamic tract. The most important point, however, is that these twitchings, though the rule in experimental monkey paralysis, were the exception in humans. The other points enumerated by Faber could all be explained on anatomical bases, totally different from those he presented in his classical monograph.

Flexner [2] has stated that the "small olfactory filaments" of the nasal area "are advantageously placed to act as the means of transportation of the virus." Faber [1] referred to the importance of the unbroken connection of the olfactory nerve, and it is here that Flexner and Lewis [3] and others have experimentally shown that absorption may take place, since they reproduced the disease by packing the nasal passages with gauze that had been soaked in poliomyelitis virus.

The olfactory nerves, consisting of unmyelinated grey fibers, with their 20 to 30 olfactory filaments, are not the only unmedullated fibers in the region of the cribriform plate, for it is precisely here that the nervus terminalis is "peripherally hypertrophied in man as compared to the known de-

velopment in other mammals." [4] The olfactory area contains approximately 1500 cells of the terminal portions of this nerve situated under the nasal mucosa, cells which with their processes make a vast interlacing network of unmedullated tissue and whose fibers *end in the ganglion terminale on the olfactory bulb.* Significant indeed is the assertion made by Brookover that the " grouping of cells and fibers " is " such as might be found in the myenteric or submucous intestinal sympathetic." [4] Most significant for us, is the similarity of the peripheral nervus terminalis to an enteric plexus.[5]

The olfactory area is peculiar in that it contains a mass of unmyelinated nerve tissue of the type which usually absorbs the poliomyelitis virus. The thirteenth cranial nerve and the olfactory fibers lie near or at the embryological upper end of the foregut at the juncture of the stomodeum. Fibers similar to the thirteenth nerve are found in the hindgut and, if morphological similarity is significant, the latter fibers should also attract the virus. The only apparent reason why the gastrointestinal tract is not seriously considered as a portal of entry for the virus is that experiments on virus transmission by way of the gastrointestinal tract have hitherto been contradictory.

Part II

Where would the portal of entry of this disease be located in the human? It is conceived that it could be any place where the virus could easily and normally come in contact with either the grey nerve fibers or the axis cylinders of medullated nerves. The disease is produced when the injection of the virus is made directly into the sciatic trunk after irritating the nerve with the injecting needle so that the axones are exposed to the virus [6, 7, 8]; when intracerebral injections are employed; when the virus is injected intraperitoneally [9]; when the virus is injected intraocularly [10]; when intraspinal [11] and intracisternal injections are made [12] and when intranasal instillation is employed—all injections having been made in locations where unmedullated fibers abound. When the gastrointestinal route has been used as a portal of entry, some isolated successes [13] and, on the other hand, many failures [14] have been reported. When one studies the rôle that the skin plays as a portal of entry, one finds that virus inunctions are relatively innocuous,[10] that it is difficult to produce the disease by subcutaneous inoculations,[15] but that infection may be consistently brought about by intracutaneous injections of the virus.[16] The unmedullated end fibers are not present in the epidermis nor to any great extent in the subcutaneous area, but they do ramify in the corium, which would be the logical place from which absorption should take place if the virus were absorbed from any spot where the naked grey fibers predominate. One could almost postulate that the virus has nearly an obligate affinity for grey nerve fibers.

An area from which absorption could take place may be present where there are grey fibers, but a " take " would depend upon an unbroken connection between the absorbing area and the central nervous system, that is, either

on the possibility that the virus could be transferred from the area of absorption to the central nervous system along an axis cylinder pathway [6] or that it could reach the central nervous system before it would be absorbed and excreted by the host. One might surmise that the rate of absorption of the virus, the ease of its transmission, its virulence, etc., would also be factors tending either to impede or to accelerate the production of the disease. The most direct routes to the brain and cord for the experimental production of the disease are by way of the olfactory and terminalis nerves, and after intrasciatic and intracerebral injections of the virus. Where the connection is definite and the course immediate, the disease is produced easily in the experimental animal. The observation could be made that, aside from a peripheral absorbing area of grey fibers or axis cylinders of medullated nerves, a convenient connection with the central nervous system must be present in the experimental animal and in the human. In this light, there are only three places in the body that could qualify as natural portals of entry, i.e., either by way of the nasal mucosa, the gastrointestinal tract, or the respiratory tract (lungs). But few experiments have been done in which the lungs have been used as a portal of entry, and confirmed evidence is lacking that would show them to be areas that would absorb the virus of infantile paralysis.

Many experimenters have tried and have failed to reproduce the disease from the gastrointestinal tract. I felt that the reason for this failure lay in the fact that the virus never approximated the grey fibers, since, after its introduction through a tube or a needle, the virus emulsion was usually swept on, out of the small intestine and into the colon. Accordingly, I exposed the abdominal cavities of monkeys, clamped the small intestine in one place with a pair of intestinal clamps a few inches above the ileocecal valve and in another place about a foot or more above this. While the clamps were held in place, a potent virus suspension was introduced into the isolated portion of the intestinal canal through a 24 gauge needle until the gut was ballooned out and the intestine was kept tense until the pinch reflex had disappeared. Poliomyelitis developed.[17]

Even though the dose had been intestinally injected, the animals might have regurgitated some virus and thus might have infected the olfactory area. Since the postganglionic fibers of the sympathetic system are unmyelinated, at least to the abdominal plexuses, and the fibers of the intestinal blood vessels are possibly unmyelinated as far as the vertebral ganglia themselves, there was no reason why the disease could not be reproduced by a subserosal injection of the virus. Accordingly, the abdomen was opened; a potent virus suspension was injected subserosally at multiple points and the disease was produced.[17] It is curious that when proper doses of poliomyelitis virus are injected subserosally, the disease that develops in monkeys is more like that seen in humans, since only a monoplegia may result, in marked contrast to the fulminating quadriplegia seen in the experimental animals after intracerebral injection or intranasal instillation of the virus.

One could surmise that the spread of the virus to the cord in such animals as developed poliomyelitis when the gastrointestinal tract was used as a portal of entry was by way of the sympathetic system.

In my clinical studies, I have observed modifications of reflexes which can be best explained as being due to an involvement of the sympathetic system followed later by an irritation of the involved somatic nerve; in short, a postganglionic lesion of the sympathetic system followed by a somatic nerve lesion.[18] That this conclusion was not unusual was shown when I studied the same reflex responses in a comparable gastrointestinal disease, typhoid fever, and found that they were involved in the same manner in the severely ill patient.[19]

In my clinical experiments, I found that following pilocarpine injection the sweat gland secretion was increased over those skin areas that corresponded to the paralyzed somatic segments. I found, also, that when those patients who had had pilocarpine injections were injected with adrenalin, sweating ceased over the skin areas of the unaffected muscles, while it continued over the segments of paralyzed nerves, indicating clearly that the thoracolumbar sympathetic system did not function for the involved segments,[20] again evidence that the sympathetic system is involved.

Monkeys injected intrasciatically with virus contracted the disease. Control monkeys whose sciatic nerves had been tied, cut and then injected with virus in the distal portion did not contract the disease. The spinal cords of monkeys were transected in the region of the tenth thoracic segment; the sciatic nerve was then injected with poliomyelitis virus and the animals contracted the disease. The spread of the virus in this case to the arms, etc., was by way of the sympathetic system, the only nerve connection not disturbed.[8] When the cord was cut and the virus injected intracerebrally, the virus was occasionally found in the distal lumbar portion, again an illustration of spread by way of the sympathetic system.[21]

Clinically, the sympathetic system is involved before the somatic, since paradoxical urinary retention with dribbling and obstinate stasis of the gastrointestinal tract often occurs before somatic paralysis is noted.[22]

For anatomical reasons, it is not illogical to assume that the virus first involves the sympathetic system in the human. The somatic nerves have no direct white fiber interpositions in the areas from the second lumbar to the second sacral segment and none upward from the first thoracic segment. Here there are immediate grey fiber connections only and it is in these segments of the cord that involvement occurs. One can hardly explain the spotty spread of a disease by a virus that travels up or down the cord and that involves first the lumbar section of the cord and then the cervical. It could be explained, however, if one presaged a spread of the virus from the gastrointestinal tract by way of the sympathetic grey fibers to the sympathetic ganglionated chain, then down to the lumbar area where no white rami are present and to the somatic nerve. In more marked involvements, the spread would be up along the sympathetic collateral chain to the only other place that lacks white rami communicantes, i.e., the cervical cord.

We should and do find most of the paralysis in the human in those muscles whose innervation comes from the lumbar and cervical enlargements. Only when the disease is massive would it involve those segments which have connector fibers (white fibers), namely, the thoracic and abdominal. Involvement of the postganglionic vagal fibers yields little clinical information, unless it be subjective. Nevertheless, in the severely toxic case, one can picture an involvement of the preganglionic vagal fibers with the upward spread of the virus, a simulation of the clinical condition of bulbar palsy.

If in the human the virus is arrested at the nerves where white fiber interpositions occur, then much paralysis would not be seen in those muscles whose innervations are below the second sacral segment. Usually the patient should be able to move the big toes, and the levator ani, coccygeus and other perineal muscles should not be affected in the ordinary case. The fingers could likewise be flexed when the arm muscles are involved. This is exactly what is usually seen in the average clinical case.

Physiologically, the early reflex changes in this disease could be best explained as an early involvement of the sympathetic system.[18] The loss of the abdominal reflex response followed by hyperactive knee jerks with or without weakness of the quadriceps muscle, in turn succeeded by loss of the knee jerk reflexes, all have their counterpart in physiological experiments. If sympathetic stimulation increases tone, how would it be affected by thoracolumbar disconnection? The muscles of sympathectomized animals are soon fatigued. Such muscles tire easily when activated, although they may be wholly under voluntary control and still have a simple somatic spinal arc intact. It is reasonable to suppose that the stability of the reflex arc and its ability to withstand fatigue, depend, to some extent at least, upon the presence of an integrated sympathetic system.

Part III

After intrasciatic, intranasal or intracerebral introduction of a virulent poliomyelitis virus in monkeys, the disease comes on within four to seven days. When I injected the virus directly into the lumbar cord itself, the animals did not become paralyzed at once, two and a half days elapsing before this condition was noted. Why should there be such a delay? The fact that the virus can be absorbed and be present in doses lethal for monkeys in the tissue of the cord, medulla and even brain long before the production of somatic paralysis in this animal is indeed peculiar. It argues for the fact that the virus, though easily absorbed by grey fibers and transmitted to the brain and cord along axonic pathways, does not immediately produce pathological changes in its passage of sufficient intensity to result in clinical evidence of disease. This is true even of the experimental animal.

Though the virus initiates the disease, there are some clinical and experimental findings which make one wonder whether the virus alone is the sole

cause of the entity known as infantile paralysis. Other diseases, such as swine influenza [23] or oroya fever,[24] are produced by a combination of factors. Perhaps poliomyelitis also is such an infection.

When I first became interested in poliomyelitis, I thought that the virus ought to be obtained easily from the feces of patients who had the disease. I tried to recover it from the stools but failed. If the virus has an obligate affinity for grey fibers, the probabilities are that it would be absorbed by the nerve fibers and stay fixed in the nerve tissue. Such virus as was not absorbed would be excreted by the gastrointestinal tract long before symptoms started and hence would not be found in the feces when paralysis came on. I found, however, that the stools obtained from patients ill with poliomyelitis during the acute stage of the disease were much more toxic than were those obtained from the same patients during convalescence. Apparently something was manufactured in the stool during the course of the disease that was more toxic to guinea-pigs; something that was not present in normal stools, and yet it was equally obvious that this something was not the virus of poliomyelitis.[25] When urine was taken from patients at the height of an attack of poliomyelitis and injected subcutaneously into guinea-pigs, the local reactions that followed such injections were more severe than those that followed injections of normal urine.

Stools collected from young monkeys were emulsified and injected subcutaneously into guinea-pigs; there were but slight local reactions. Stools collected from the same monkeys after they had contracted infantile paralysis showed a very definite increase in toxicity in that the abdominal areas of the guinea-pigs injected with this emulsion might slough and the animals might even die.[26]

It occurred to me that a secondary factor must be present before the clinical condition of infantile paralysis could be produced. The colon bacillus was considered in this light. I studied the agglutination titer value contained in the blood serums of poliomyelitis patients, taken at the height of the disease and later during convalescence, and found that there was a marked difference, since the agglutination titer was much less for the enteric group in the serums taken at the height of the disease than it was for those taken during convalescence.[27] It was not possible at the time to say whether the agglutination titer values were lowered with disease and returned to normal with recovery, or whether the titer was lowered before the disease occurred and increased with recovery.

The young macacus Rhesus monkey is very susceptible to poliomyelitis and has little or no agglutinins in the blood serum against the colon bacillus. Curiously, as the animal gets older, its serum agglutinin titer for colon organisms becomes higher. It is also curious that such animals become more refractory to the same unit dose of virus as they grow older. I immunized young monkeys artificially in order to increase their titer value and then injected them with potent poliomyelitis virus. When they contracted the disease the agglutinin titer of their blood serum decreased, and im-

POSSIBLE METHOD OF VIRUS SPREAD IN INFANTILE PARALYSIS

Phase	Position of Virus	Symptoms
I.	At first the virus is free in the gastrointestinal tract.	There are none; or possibly some with diarrhea and pain.
II.	The virus becomes fixed in the unmedullated postganglionic fibers of the thoracolumbar outflow.	The abdominal reflexes are absent or modified. There is constipation possibly, indefinite pain in the belly. There is pain over the back too.
III.	The virus spreads from the sympathetic system to the somatic segmental nerve.	In addition to the symptoms described in Phase II, there is hyperactivity of the reflexes with tiring on repeated stimulation.
IV.	The virus, spreading backward over the somatic segmental nerve, reaches the spinal ganglia.	In addition to the symptoms described in Phases II and III, there is segmental pain in the muscles and tendons that are supplied by the nerve of the segments involved.
V.	About this time, the virus begins to be absorbed and excreted by the urinary bladder.	A peripheral type of urinary bladder paralysis may now appear with overflow dribbling when the virus factors present are absorbed by the terminal grey fibers of the bladder and its neck, whether of the sympathetic or parasympathetic system.
VI.	The virus reaches the cord and involves the anterior horn cell.	In addition to the symptoms described in Phase V, the reflex reactions now become diminished or lost. Muscle paresis or paralysis appears.
VII.	The virus travels up the sympathetic chain to involve the cervical area.	Here the train of events is the same as outlined in Phases III and VI.
VIII.	The virus may be virulent enough to be absorbed directly by the vagus nerve.	A condition simulating bulbar palsy appears. There is dysphagia, dysarthria, etc.
IX.	The virus may travel along the grey fibers of the sympathetic system, or by a cord pathway to the medullary, the internal capsular and the cortical areas.	The symptoms here would depend upon the localization of the virus, with bulbar palsy, hemiplegic and encephalitic reactions, respectively.

mediately before their death the agglutinin titer value was practically nil. From the results found in the human and from those obtained in experiments with monkeys, it may be inferred that the agglutinin titer for the colon group is depressed during the acute stage of the disease.[27]

The idea that the enteric organisms have some part to play in the production of this disease was further bolstered by the fact that the monkeys which had been actively immunized had a definite, though incomplete, nonspecific protection, since a longer time interval elapsed before the protected animals contracted the disease.[28]

Other things point to the fact that the resident enteric bacillus, whether paratyphoid A or B, or some form of colon organism, may be a secondary

factor in the cause of this infection. The fact that the glands of the mesentery are enlarged is not an evidence of a general infection, but may merely indicate that the area of the intestine that they drain is involved, as would be expected in a stased gut.

There is a lymphocytic reaction and a response in the glandular elements that is typically of a typhocoli nature. A distinct leukopenia and a relative lymphocytosis would be the expected result from an infection caused by such a close generic relative of the typhoid organism, as the colon or the paratyphoid bacillus. Such a blood picture in poliomyelitis has been described by Müller,[29] Taylor [30] and Gay and Lucas,[31] though the figures of the latter have not been completely accepted by Peabody, Draper and Dochez.[32] The most complete and accurate observations on the blood count in experimental poliomyelitis have been those made by Harmon, Shaughnessy and Gordon.[33] They reported that in the stage of prostration there is always a marked drop in the white cell count to a point far below the normal for a given animal, a leukopenia with both lymphocytes and polymorphonuclear neutrophilic leukocytes participating. They could not confirm the opinion that a change in lymphocytes with a leukopenia was a characteristic experience in the stage prior to the appearance of paralysis. In most of their experimental animals, there was a preparalytic increase in neutrophilic leukocytes coincident with a rise in body temperature and a corresponding drop in circulating lymphocytes, a drop frequently of sufficient magnitude to mask the leukocytosis when only the total number of white cells was observed. An initial transient leukocytosis was noted by these authors within a few days after the injection of the virus. I have been able to confirm these findings in duplicate studies.[34] During the latter stages of the disease, the lymphocytes seem to be withdrawn from circulation. This would fit in well with the advent of local intestinal stasis with the accumulation of intestinal toxins.

Osler's observations that a state of poliomyelitis occurred in typhoid fever with the symptoms of acute ascending paralysis are pertinent to our point.[35]

Other suggestive evidence lies in the consideration of morbidity curves of infantile paralysis in relation to season. When these curves were studied, it was found that they may be practically superimposed on dysentery curves.[36] Aycock and Eaton [37] have described a spring and summer peak of poliomyelitis morbidity and have noted that the curves occur about the same time as do those for the spring and fall epidemics of typhoid fever.

In China with its teeming millions, where dysentery and gastrointestinal diseases abound, but one case of poliomyelitis was reported in Peiping Union Medical College Hospital among 25,000 admissions. In the southeastern part of the United States where gastrointestinal diseases are more common, the disease is not so prevalent though it is not entirely absent. It is a disease which is more apt to be found in those countries of the globe where dysentery or gastrointestinal diseases are not a very common factor in the weekly morbidity and mortality reports.

From the facts related, one could surmise that a dual condition of immunity may exist against this disease in the human. One person may have a high degree of protection against the gastrointestinal group of organisms and their toxins, and even though the virus is taken into the gastrointestinal tract, the individual may never become ill with the disease. On the other hand, another person may be sensitive to the typhoid-paratyphoid or to the colon bacillus factor, but immune to the virus, and thus never contract the disease.

This explanation of the mechanism of the production of poliomyelitis in the human, based on anatomical, pharmacological and experimental evidence, is one that is essentially consistent with all the vagaries of the disease.

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GASTRIC DIGESTION

A SIMPLE VISUAL TEST, AND IN VITRO STUDIES *

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Until we arrive at a stage where foods may be concentrated and sufficiently predigested to allow of administration to human beings in very small quantities, studies of digestion will continue to be of extreme importance. Protein digestion is the outstanding function of the stomach, but the uncertainty and incompleteness of our knowledge concerning gastric function are attested to by the variety and multiplicity of tests for evaluating gastric digestion. These are familiar to everyone interested in gastrointestinal function, and do not need reiteration.

Some years ago, it became apparent to the senior author that the usual clinical methods of evaluating gastric digestion were far from satisfactory. The work of Schmidt [1] seemed to offer a more promising approach to this problem than any of the other procedures in use. The method of this investigator consisted in administering to the patient small gauze bags containing ground beef muscle and spleen. These bags were subsequently recovered in the stool, following which the contents were stained with methylene blue and examined microscopically. The extent of gastric digestion was determined by the intensity of the action of pepsin-HCl on the connective tissue binding the muscle fibers, while the pancreatic or tryptic digestion was indicated by the extent of dissolution of the transverse striae of the muscle fibrils and the nuclei of the sarcoplasm and splenic cells.

For some time it has been the experience of one of us (M. B. L.) that this microscopic method of estimation of gastric function (digestion) is superior to the variable gastric analyses for routine diagnostic work. The progress of improvement or retrogression of digestion under the influence of oral administration of pepsin and acid could be well followed by this method. However, certain suppositions made by Schmidt concerning the secretions involved in the digestion of the various tissue elements present in the test meal have been found to be erroneous. In the course of investigations on this point, certain other observations of interest concerning digestion have been made.

Clinically, it has been noted consistently that administration of pepsin-hydrochloric acid to patients with subnormal digestive capacity caused the digestion of the connective tissue binding the muscle fibers, as stated by Schmidt. In addition, however, it was found that the nuclei also were completely dissolved, while even more striking was the complete obliteration of the cross-striations of the muscle fibrils when gastric function was thus restored to its normal level. In view of the fact that the microscopic esti-

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mation of gastric function is dependent upon the type of elements attacked as well as the degree of the digestion, it seemed an important point to attempt to confirm these observations under conditions more easily controlled than those prevailing in the animal body. Tests were carried out in vitro, with various combinations of gastric secretions in the form of scale pepsin and intestinal secretion in the form of pancreas-bile (combination) along with HCl. The action of these materials was tested on representative types of muscle tissues, including those of beef, pig, fish, fowl and crustacean. The results obtained in some of these tests are indicated in table 2.

Several points of interest resulted from the observations shown. The fact that the nuclei and the striae of the muscle tissues were visibly as well digested as the connective tissue by the pepsin-HCl alone is shown in accompanying photographs. The complete inactivity of the intestinal secretion alone on these elements is likewise illustrated, and offers a striking comparison to the activity of the gastric enzyme. Figure 1*a* illustrates partial digestion of the muscle fiber of a dried beef preparation by the action of pepsin-HCl for 120 hours. In figure 1*b* the striae and nuclei are seen to be almost completely digested, while in figure 1*c* these elements are completely digested. As contrasted with this, figure 1*d* illustrates the result of exposure to the intestinal secretion alone for 120 hours, and as demonstrated, the fiber is not affected in any way so far as the striae are concerned. The nuclei also were unaffected, but were not visible because of the lack of enzymatic action on the striae. This point has been proved by addition of pepsin-HCl to tubes containing pancreas-bile (combination) which had been totally ineffective after 96 hours. Following the addition of the gastric ferment, the striae were obliterated and the heretofore untouched nuclei became visible during the period before they too were destroyed. As expected, neither pepsin nor HCl alone exerted any action on the muscle fibers. It is evident, therefore, that pepsin-HCl in combination is the sole digestant of these elements.

As a routine procedure in the clinical application of these results, an arbitrary basis has been chosen for the expression of the degree of gastric digestion. A count is made of the relative numbers of completely digested muscle fibers, i.e., those in which the striations are absent (nuclei, of course, are not seen in stool specimens) and of the undigested fibers, which have retained their original markings. The proportion is then indicated in terms of per cent of digestion. Thus:

100 per cent digestion—all fibers digested, as in cases of hyperacidity.

80 per cent digestion—digested to undigested fibers in the ratio of 80:20. As the result of observations on many patients, this is considered the normal level of digestion.

10 per cent digestion—indicates practically an anacidity. The allowance of one digested fiber out of 10 is made to cover the accidental factor involved in microscopic work.

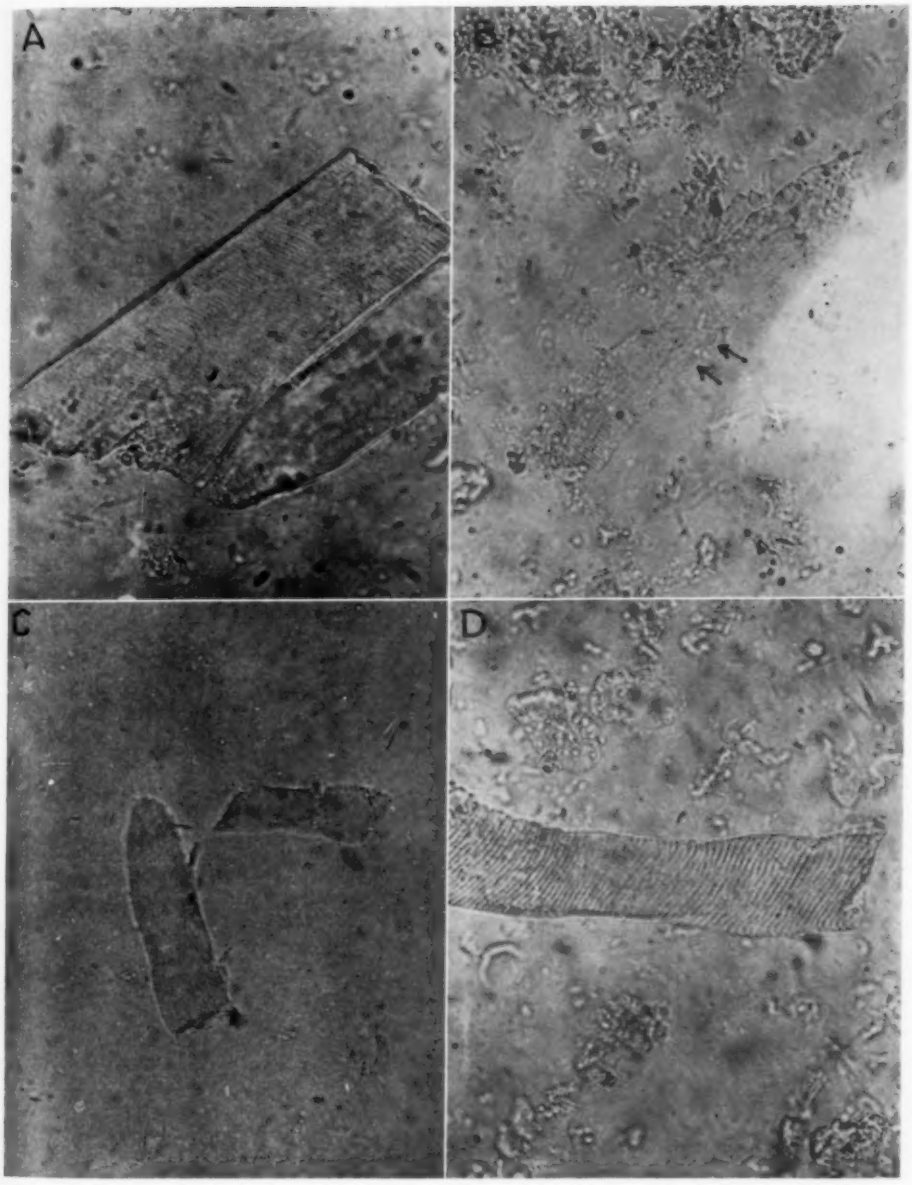

FIG. 1. Digestion of powdered beef by pepsin-HCl in vitro. (*a*) Partial fiber digestion after 120 hours. (*b*) Partially digested striae and swollen nuclei. (*c*) Complete digestion of striae and nuclei. (*d*) Beef in intestinal secretion (pancreas-bile combination); undigested.

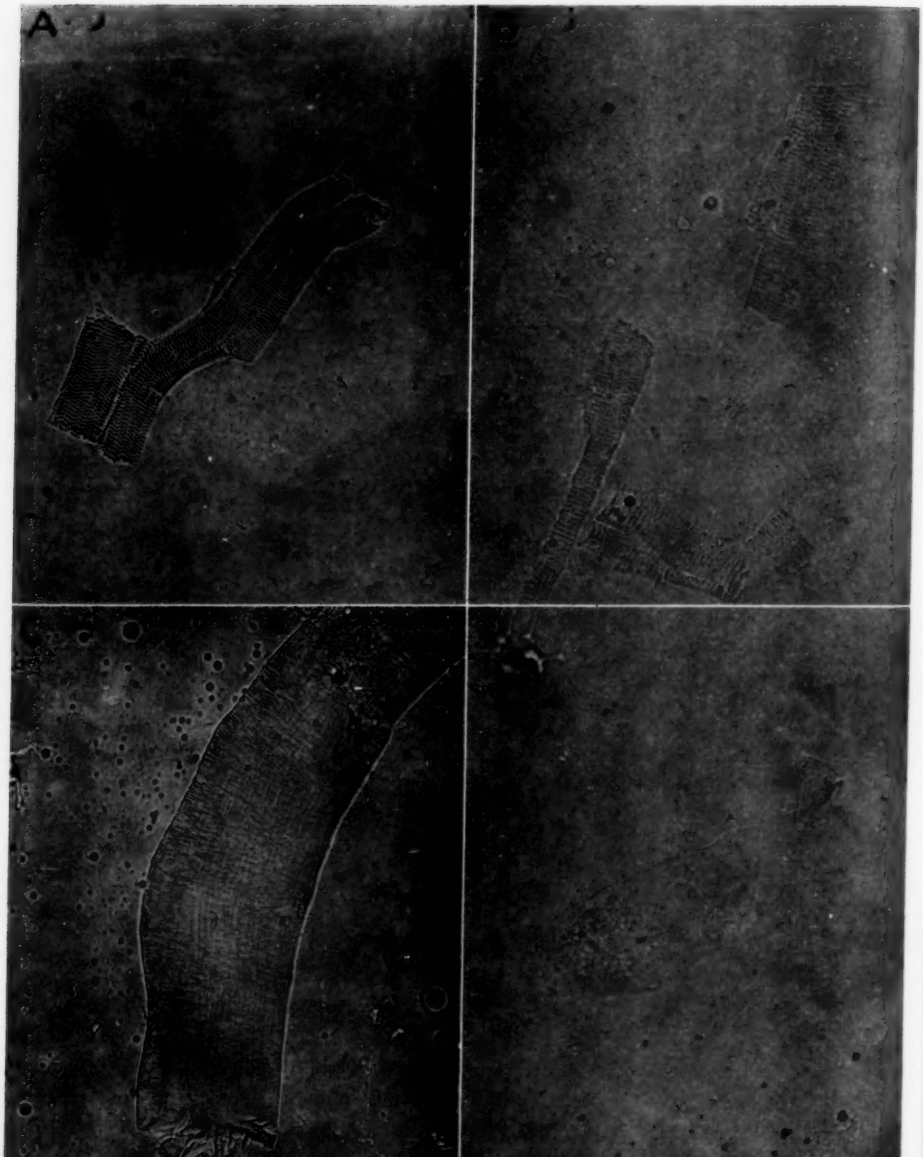

FIG. 2. Digestion of fish fiber and crab fiber in vitro. (*a*) Crab fiber after 120 hours in pancreas-bile combination, with Na_2CO_3. (*b*) Crab fiber after 120 hours in pepsin-HCl. (*c*) Fish fiber after 72 hours in pancreas-bile combination, with Na_2CO_3. (*d*) Fish fiber after 72 hours in pepsin-HCl.

In the use of any set of values which the clinician may choose as a matter of personal convenience, account must be taken, of course, of these fibers which show only partial digestion. After some experience with the method, however, it will be found that such intermediate stages may be averaged with the completely digested and undigested forms with little difficulty. After a short period of observation, the physician may readily determine the degree of gastric digestion for practical purposes without the necessity of recourse to the stomach tube, with its attendant disturbances of the functional normality due to anticipation of the test.

In table 1 are given typical case reports illustrating the relationship between the values obtained in gastric analyses and the extent of digestion indicated by the microscopic method of stool examination.

TABLE I

Name	Free HCl	T.A.	G.I. Meat Digestion
N.B.	0°	4°	10%<
S.C.	0°	4° and 6°	10%<
L.A.	18°	34°	50%
I.S.	24°	51°	80%
C.E.	66°	82°	90%>
S.S.	55°	80°	90%>

A striking fact which appeared during the course of the work, summarized in table 2, was that under certain conditions, mixtures of gastric and duodenal secretions showed definitely better digestive abilities than either of these factors alone. This increased activity was manifested not so much as a more extensive digestion, though this was increased in most cases, but rather as a much more rapid process than that obtained with pepsin-HCl. Tubes 4 and 5, table 2, illustrate this point. The question arose as to whether the difference in action between these tubes and tube 1 (pepsin-HCl) was due to the enzymatic constituents present in the former, or to the difference in pH between the tubes. Menten, quoted by Howell,[2] obtained a pH of 1.0 for normal gastric juice, using hydrogen gas electrodes. Experiments by other investigators have shown, however, that an acidity this high is not favorable for the digestive action of pepsin. Thus, Michaelis and Davidsohn have stated that the optimum acidity for peptic action is at pH 1.6; when the HCl is combined in the stomach, the pH is 3.0, and at this concentration, the digestive action of pepsin is relatively feeble. As shown in table 2, the pepsin-HCl mixture was at a pH of 0.9, whereas tubes 4 and 5 were at pH 1.2 and 2.9 respectively. It was considered an important possibility that this difference in acidity might of itself account for the variation in digestive activity by the pepsin, regardless of the other enzymatic constituents of the tubes. Furthermore, it is generally thought that normal peptic activity is counteracted on contact of the gastric and duodenal contents, either in the normal manner or by regurgitation of duodenal contents into the stomach. For these reasons, further experiments were undertaken

TABLE II
Action of Gastric and Intestinal Secretions Alone and in Combination on Muscle Fiber

Tube		1	2	3	4	5	6	7	8
Digestive enzymes in tube		Pepsin † + HCl	Pepsin	Pancreas-Bile (comb.)	Pepsin + HCl + Pancreas-Bile (comb.)	Pepsin HCl + Pancreas-Bile (comb.) Na_2CO_3	Pepsin + Pancreas-Bile (comb.)	Pancreas-Bile (comb.) + HCl	Pancreas-Bile (comb.) + Na_2CO_3
pH*		0.9	3.5	7.3	1.2	2.9	4.9		10.11
Muscle fiber used and extent of digestion microscopically.	Beef	70%	20%	0	90%	90%	20%	0	0
	Fish	50%	10%	0	60%	40%	10%	0	0
After 24 hrs.	Powd. beef	75%	35%	0	90%	70%	50%	0	0

* pH determined by quinhydrone electrode method.

† It was noted that the activity of the pepsin-HCl depended upon its quantitative combination. Variation of the pepsin, of the HCl, or of the meats within limits altered the rapidity and degree of digestion. Clinically, it was found that beef up to 2½ times the quantity normally given was digested to the same degree (50%, 60%, etc.) as the average amount, as determined by stool examination, indicating that the reaction to an increased demand for gastric secretions is quantitative rather than qualitative.

to determine the effect of the hydrogen-ion concentration on the digestive activity of these combinations. In table 3 are shown tubes containing different mixtures of enzymes, acid, and muscle fiber, neutralized with Na_2CO_3 at intervals before and after contact with the various meat fibers tested.

The results recorded surprisingly demonstrated that duodenal content on contact with the pepsin-HCl immediately activated peptic digestion to a striking degree, with a rapidity several times that shown by the pepsin-acid alone. This was true when the pepsin-HCl was mixed with duodenal secretion and the test meat before neutralization (to pH of 7.0) with Na_2CO_3, which was carried out 15 minutes later as shown in tube 6. On the other hand, if neutralization of the pepsin-HCl and pancreas-bile (combination) was carried out immediately before the meat was added, digestion was very greatly reduced. Almost no digestion at all was obtained if the pepsin-HCl was neutralized before being combined with the pancreas-bile (combination) and meat. It is thus seen that if contact was permitted between pepsin-HCl and pancreas-bile and the meat for even 15 minutes, then complete neutralization was almost wholly ineffective in curtailing the digestive activity. As shown in table 2, pepsin and pancreas-bile (combination) alone were inactive. Work on individual intestinal factors causing activation is now in progress.

It is very interesting and suggestive to attempt an application of these in vitro observations to the conditions existing in the gastrointestinal tract. Abderhalden and Meyer,[3] quoted by Hawk (Sixth Edition, page 142), have shown active pepsin to be present in the contents of all parts of the small intestine. It is suggested that pepsin may be adsorbed in the stomach by such protein substances as pass into the intestine in solid form and that the pepsin thus protected may bring about gastric digestion whenever the reaction of the surrounding intestinal contents is favorable. This fact may be of importance in connection with the profound proteolysis taking place in the intestine. Heretofore this process was believed to be furthered by trypsin and erepsin alone. Furthermore, the immediate activation of digestive activity by the contact of the gastric with the duodenal secretions may offer an explanation as to one of the chief reasons why duodenal ulcer, a condition in which there is usually a gastric hyperacidity, is found so much more commonly than gastric ulcer. It may also offer an explanation as to why certain types of operations for duodenal ulcer, which permit the free admixture of gastric and duodenal contents, may in a number of instances be ineffective as regards cure, and even permit the formation of additional postoperative ulcers at the site of operation. In addition, from the medical standpoint of treatment for gastric and duodenal ulcer, the findings presented in table 3 would indicate that unless the pepsin-HCl is neutralized completely before combining with the duodenal content, digestion of the ulcer would not be prevented sufficiently to allow healing to take place. Methods of treating gastric and duodenal ulcers might be modified to take care of these facts to a better degree than is now the case under the Sippy

TABLE III
Effect of pH on Action of Gastric and Intestinal Secretion on Muscle Fiber

Tube	1	2	3	4	5	6	7	8	9	10
Digestive enzymes in tubes	Pepsin-HCl	Pepsin-HCl + Pancreas-Bile (comb.)	Pepsin-HCl + Pancreas-Bile (comb.) added after 30 minutes	Pepsin-HCl + Pancreas-Bile (comb.) added after 75 minutes	Pepsin-HCl + Pancreas-Bile (comb.) added after 15 minutes then neutralized	Pepsin-HCl + Pancreas-Bile (comb.) (mixture neutralized with Na_2CO_3 after 15 minutes)	Pepsin-HCl + Pancreas-Bile (comb.) neutralized immediately	Pepsin-HCl + Pancreas-Bile (comb.) neutralized immediately	Pepsin-HCl (neutralized after 15 minutes)	Pepsin-HCl + Pancreas-Bile (comb.)
Time of addition of beef to tubes	immediately	immediately	immediately	immediately	immediately	immediately	Beef added after Pancreas-Bile (comb.) and before neutralization	Beef added immediately after neutralization	immediately	immediately
pH of mixtures*	0.9	1.2	1.2	1.2	1.2	1.2	1.2	1.2	0.9	4.9
Results (per cent) after 24 hour digestion	70%	90%	80%	70%	30%	50%	0	0	20%	10%

* pH determinations by quinhydrone electrode method. The pH's given in the cases where neutralization was carried out refer to the acidity before such treatment.

treatment, or the Leube, Lenhartz or other methods of treating ulcers, which have a limited percentage of success. It seems suggestive from the experiments reported that neutralization of the gastric content by means of potential or active alkalies before combination with any foods is essential for the prevention of digestion of the gastroduodenal content as well as of the duodenal wall, since even 15 minutes of exposure to gastroduodenal secretions at the proper pH is sufficient to allow a certain degree of digestion of both. Recently, one of us (M. B. L.) has carried out this procedure in the treatment of active duodenal ulcers, and the results thus far have been gratifying. The method consists in the administration of potential alkalies such as powdered $CaCO_3$ *just before feedings*, and of other alkalies after the meals, so that they may be "on hand" for neutralization of the secretion as manufactured as well as for subsequent neutralization of any later excess. This treatment may be employed in conjunction with any of the usual therapeutic measures employed in this condition. Doses of 1/2 to 1 drachm of alkali are administered before the meal, in addition to the usual doses of alkalies after feeding. Digestion of meat fibers, as demonstrated by our method of stool examination, is limited to 10–20 per cent, alkalies being raised or lowered as desired through this microscopic means of control.

In conjunction with the work reported, it was decided to extend the studies of digestion to include a point which is of much clinical interest to the gastro-enterologist. In the human being, animal protein is much more readily digested than the proteins of vegetables. Unpublished data of the senior author point to such a conclusion, and Munk [4] has shown that whereas the easily digestible animal foods are absorbed to the extent of 97 to 99 per cent, the utilization of vegetable foods is less complete. This difference is ascribed to the presence of the indigestible cellulose in vegetable foods, rather than to any peculiarities of the proteins. Recently, the same conclusion has been drawn by the British experts of the Interallied Scientific Food Commission.[5] It was thought that since in certain conditions, such as esophageal carcinoma, a conveniently administered and easily digested form of animal protein is highly desirable, a comparative in vitro and in vivo study of the digestion of various types of meats would be profitable. For this purpose, cooked fish, beef, pork, lamb, veal, crab, and chicken were used. In addition, a preparation of powdered beef * containing 10 per cent powdered liver, ground celery seed, and the salts of calcium, magnesium, sodium, potassium, etc., added in quantities to bring these elements to the level of the normal requirements, was used.

In the stools of individuals with normal digestive ability, it has been found that non-oily types of cooked fish were most easily digested, the preserved type of bacon and fried or cooked crab were most difficult to digest, while beef and fowl occupied intermediate positions of digestibility. The results obtained in test tube experiments may be seen in figures 1 and 2, which are representative examples of the action of pepsin-HCl on these

* This preparation was furnished through the coöperation of the experimental department of the Valentine Meat Juice Corporation of Richmond, Va.

cooked fibers. The crab is shown before digestion and after 120 hours in pepsin-HCl at room temperature; it will be noted that only partial digestion has occurred. Under the same conditions, the fish is seen to be completely digested, as is also the powdered beef.

Since the dried beef-liver was found to undergo digestion as well as ordinary cooked beef, this preparation has been put to practical use in various types of cases with very satisfactory results. Suspended in water, bouillon or other liquid vehicles, it has been injected through a duodenal tube with syringe, without fear of blockage. In cases where difficulty was experienced in swallowing lumpy masses due to throat affections or following tonsillectomy or tooth extraction, in infants and children when a convenient form of beef easily administered in a fluid medium was required, in forced feeding cases, and in adults or children in whose diets carbohydrates and fats could not be raised, but in whom an increase of bulky proteins beyond a certain quantity was nauseating, this preparation has been successfully employed.

Summary and Conclusions

1. A microscopic method of estimation of gastric digestion based on the demonstrated ability of the gastric secretions to digest striae, connective tissue and nuclei, has been found to furnish a satisfactory index of gastric function (digestion).

2. The mixture of secretions derived from the duodenum when combined with pepsin-HCl promotes the rapidity of digestion to a marked degree. Such increased activity occurs if the components are allowed to act on the test material at an appropriately low pH. Under these conditions, neutralization of the acid after a short period inhibits the progress of the digestion to some degree only. When neutralization of the mixture is effected before it has come into contact with the test material, however, no digestive activity is manifested. On the basis of these observations, it is suggested that large doses of alkali be administered both before and after meals in cases of duodenal ulcer.

3. Simultaneous experiments on the comparative digestibilities in vivo and in vitro of various animal proteins in the form of representative meats have indicated that a dried beef-liver preparation is of value in cases where such proteins are desired but cannot be conveniently taken in the usual manner.

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EDITORIAL

PHYSIOLOGICAL AND CHEMICAL RELATIONSHIPS OF THE SEX HORMONES

ALMOST all of our chemical and physiological knowledge of the estrogenic hormone has been acquired within a decade. Credit for this progress belongs to many workers. The stimulus which has produced such rapid development was furnished primarily by important studies. One was reported by Allen and Doisy late in 1923 when they showed that the injection of alcoholic follicular extracts from hog ovaries would bring about estrus in castrated mice or rats.[1] The second advance was made by Aschheim and Zondek in 1927,[2] when they demonstrated a substance in the urine of pregnant women which conformed in all of its biological effects to the material found earlier in the follicular fluid. This discovery opened up the way to productive chemical investigation, because it pointed to an abundant source of the material, which was free of proteins and lipoids, thus greatly facilitating the work of extraction. In 1929 its isolation in crystalline form was announced by Doisy [3] and almost simultaneously by Butenandt.[4]

The essential chemical configuration of the female sex hormone is that of a condensed carbon ring compound composed of three six-membered rings, together with a five-membered ring attached at one end. It is a derivative of phenanthrene. The condensed carbon ring compounds, as sterols, occur also in cholesterol and its derivatives, the bile acids, as well as in ergosterol, and hence, in vitamin D. As is now believed, the same essential characteristic structure also occurs in the closely related male sex hormone as well.

The clinical value of the estrogenic hormone has not been seriously regarded up to the present time. Certain reports made almost within the year may now serve to change this attitude materially. It appears that rather large amounts of the material, which have not been obtainable until very recently, are necessary to bring about clinical effects in woman. Kaufmann has recently reported that menstrual changes can be produced in the castrated woman with a dose of approximately one million rat units.[5] Much larger doses, five-fold, spread over a period of weeks, will produce an actual glandular cystic hyperplasia. This work, which has in part been confirmed in England, was rendered possible by the interesting discovery that a com-

[1] ALLEN, E., and DOISY, E. A.: Ovarian hormone; preliminary report on its localization, extraction and partial purification, and action in test animals, Jr. Am. Med. Assoc., 1923, lxxxi, 819–821.

[2] ASCHHEIM, S., and ZONDEK, B.: Hypophysenvorderlappenhormon und Ovarialhormon im Harn von Schwangeren, Klin. Wchnschr., 1927, vi, 1322.

[3] DOISY, E. A., THAYER, S., and VELER, C. D.: Preparation of crystalline ovarian hormone from urine of pregnant women, Jr. Biol. Chem., 1930, lxxxvi, 499–509.

[4] BUTENANDT, A.: Naturwissensch., 1929, xvii, 879.

[5] KAUFMANN, C.: Therapeutics with hormones of ovary, Proc. Roy. Soc. Med., 1934, xxvii, 849–863.

pound elaborated synthetically from the hormone itself, by the addition of two atoms of hydrogen will increase its activity several fold.[6] If further hydrogen atoms are added, the compound loses its estrogenic activity, and if six more be attached, it is said, it develops properties of the male sex hormone.

The strict specificity of the female sex hormone has been rendered dubious, indeed, in the light of several lines of investigation. It has been known for some time that certain vegetable extracts possess the property of provoking estrus in rodents exactly as does the estrogenic hormone.[7] Conversely, a few milligrams of crystalline folliculin when placed in water surrounding hyacinth bulbs will hasten remarkably the floral development.[8] Butenandt, again, has demonstrated the identity of the phytohormone derived from palm fruit, and obtained in crystalline form,[9] with the estrogenic hormone. Another group of compounds with estrogenic activity was produced last year by Aschheim and Hohlweg,[10] who used coals, asphalt and petroleum oils as their starting point. They made the ingenious suggestion that the substance in coal might be the variety of the estrus hormone known to be present in plants, and suggested that it originated in the primeval, coal producing forests. Dodds [11] and Cook and their associates last year reported studies on compounds derived from phenanthrene which is obtained from coal tar. These differ in structure from the natural estrogenic substances in the absence of the attached five carbon ring, but at least one member of the series of derivatives studied possesses even greater potency than one of the natural estrogenic agents recovered from pregnant urine. Not only are these observations of great general interest, but they possess practical therapeutic potentialities as well. In two instances these compounds have been shown to have besides their estrus-producing power, another characteristic property of the naturally occurring sex hormone, namely, that of causing a reversion of the plumage of the brown leghorn capon to the female type. So far as is known, these somewhat simpler compounds, differing materially from the natural estrus-producing hormone, possess all of the known types of activity of the latter. Such observations cast doubt on the specificity of this natural hormone, and may offer a better explanation of the origin of the active substances derived from bitumens. Substances producing tar cancer have also a related structure and in one or two instances also have been shown to have feeble estrogenic activity.[11]

Finally, vitamin D is also a member of the condensed carbon ring group

[6] SCHWENK, E., and HILDEBRANDT, F.: Naturwissensch., 1933, xxi, 177.

[7] LOEWE, S., LANGE, F., and SPOHR, E.: Über weibliche Sexualhormone (Thelytropine); brunsterzeugende Stoffe (Thelykinine) als Erzeugnisse des Pflanzenreiches, Biochem. Ztschr., 1927, clxxx, 1–26.

[8] SCHOELLER, W., and GOEBEL, H.: Die Wirkung des Follikelhormons auf Pflanzen, Biochem. Ztschr., 1931, ccxl, 1–11.

[9] GIRARD, A.: Bull. Soc. Chim. Biol., 1933, xv, 581.

[10] ASCHHEIM, S., and HOHLWEG, W.: Über das Vorkommen östrogener Wirkstoffe in Bitumen, Deutsch. med. Wchnschr., 1933, lix, 12–14.

[11] DODDS, E. C.: Hormones and their chemical relations (Goulstonian lecture), Lancet, 1934, i, 987.

of compounds, and a study of several sterols allied to ergosterol has shown these to have estrus-producing properties, most marked in the case of neoergosterol, but definite in the case of ergosterol itself, as well as in that of the closely related vitamin D.[11] The amount of the latter required to produce estrus is very large in relation to the amount needed to protect against rickets, but the estrus changes take place before any signs whatever are seen of hypervitaminosis. A single substance, therefore, has been shown to possess two entirely distinct physiological properties, one characteristic of a vitamin (antirachitic) and one of a hormone (estrogenic). It seems quite clear that further study of the sterol group in its relation to animal metabolism furnishes a promising field not only for advancing knowledge of the mechanism of vitamin and hormone action, but for the discovery of compounds of possible therapeutic value as well.

GEORGE A. HARROP

REVIEWS

The Compleat Pediatrician. Practical, Diagnostic, Therapeutic and Preventive Pediatrics. By WILBURT C. DAVISON. The Duke University Press, Durham, N. C. 1934. Price, $3.75.

Here is a book out of the ordinary which starts out with a clever adaptation of the title page of Isaak Walton's Compleat Angler. The author was for some time the acting pediatrician to the Johns Hopkins Hospital and now fills the chair at Duke University. It is a book primarily for the medical student and the busy practitioner, and it has been kept small enough to be put in the bag of the pediatrician along with such necessities as the stethoscope and otoscope. It is divided into various parts setting forth the signs and symptoms, the various diseases, the laboratory tests, the preventive measures and the treatment and prognosis.

If the student knows the principal signs and symptoms he may, by consulting the book, find out in which conditions they are found and then, by using the cross references, learn what is to be done to prevent or cure. There are numerous tables showing the development of the child, diagnostic aids, foods, drugs and what not so that in one small volume one may have the cream of pediatric knowledge, very much condensed it is true, but all there. The amount of labor which went into the making of this book was certainly very great; it occupied the spare time of eight years, and well it might. Only those with encyclopedic memories can call to mind the many details which are in daily use. This book will help those of us who are not so endowed.

Among other things we learn that of the 307 diseases to which children are heir, only 100 are important, that is the 37 which cause 56 per cent of the deaths in children and which are preventable, and the 63 which are responsible for 21 per cent of the pediatric deaths and which respond to adequate therapy. One may question placing allergy and epilepsy in this group. When the author adds automobile accidents and suggests teaching children at home or if they are in school to take constant precautions one has to smile. Nevertheless the book is a real contribution and may be recommended most highly for just what it claims to be, a help to the student and to serve as a vade mecum for the practitioner. The author is to be congratulated.

J. H. R.

Medicine in Canada. Clio Medica Series. By WILLIAM BOYMAN HOWELL, M.D. xiii + 137 pages; 11.5 × 17 cm. Paul B. Hoeber, Inc., New York. 1933. Price, $1.50.

Canada has had several medical historians of note including J. J. Haegerty, H. S. Birkett, M. R. Charlton and Maude E. Abbott, and now comes Howell with this little volume in the Clio series. Starting with Jacques Cartier and his experience with scurvy which happened in 1535 the author comes down through the years at a rather startling pace and winds up about 1870, using short chapters either biographical or regional. It seems a pity that he did not add a few pages and bring it down to date, for a history of medicine in Canada without the name of Osler in it seems an oddity. Those were brave days when Bonnerme, surgeon to Champlain, narrowly escaped being hanged for having been implicated in a plot to kill the leader. The plotters were apprehended while trying to decide whether they should shoot or strangle him. An interesting little book.

J. H. R.

Davis' Applied Anatomy. Ninth Edition. By GWILYM G. DAVIS, M.D.: revised by GEORGE P. MULLER, M.D. 717 pages; 26.5 × 19 cm. J. B. Lippincott Co., Philadelphia. 1934. Price, $9.00.

This book, in its ninth revision since 1910, needs no new recommendation. The present edition preserves the excellent form and typography of the old, and many sections have been entirely rewritten. The author of this revision, Dr. George P. Muller, has been assisted by several surgical specialists all of whom have maintained a high standard in their various sections. Eighty-six pages have been added which are chiefly devoted to the applied anatomy of special surgery. There are also many new illustrations.

In the light of the general excellence of this edition, the reviewer hesitates to mention occasional errors in labeling, such as are seen in distinguishing the inguinal fossae, on page 441, and the omission of a designation, on page 443. The description of the fascial spaces in the hand might also have been enlarged upon to advantage.

The subject matter is, as in other editions, a very good example of the use of mature judgment in selecting the material which fills the gap between anatomy and surgery.

E. M. H., JR.

Tumors of the Female Pelvic Organs. By JOE VINCENT MEIGS, A.B., M.D., F.A.C.S., Instructor in Surgery, Harvard Medical School; Surgeon to Out-Patients, Massachusetts General Hospital; Associate Surgeon, Collis P. Huntington Memorial Hospital; Surgeon, Pondville Hospital, Massachusetts State Cancer Hospital. 533 pages; 24 × 16 cm. Macmillan Co., New York. 1934. Price, $6.00.

This work will be of interest to all students of medicine and particularly so to the gynecologist, pathologist and radiologist. The subject is clearly and painstakingly presented and shows the care with which the material has been evaluated.

The first five chapters deal with carcinoma of the cervix and carcinoma of the body of the uterus and the excellent presentation of this phase of the work follows the general plan carried out in the remaining chapters.

First, there is a general discussion of the subject which is followed by the pathology of the tumors of each organ and to this is added the symptomatology manifested by the lesion. The author then presents a statistical report of his series of cases which, although small in number, are of value due to the thoroughness with which they have been studied. The methods of treatment, especially by radium and x-ray, are clearly presented in detail. The author correctly states that there are two methods of treating cancer of the cervix, surgery and radium, and that in all but the very early cases surgery should be abandoned. He further states that this study has shown that surgery will cure some cases of carcinoma of the cervix with lymph node involvement and there is reason to believe that radium will not. This latter statement is, however, debatable.

The chapter on Tumors of the Ovary, comprising 110 pages, is well presented. The text is clear, easily readable, and the illustrations are good. The section on embryonal tumors, including the feminizing and masculinizing group, is of particular interest.

The final chapter devoted to metastases occurring throughout the body, chiefly from the cervix, body of the uterus, and the ovary, is most instructive.

At times the text is prolix, due to repetition, but in such a statistical study this is difficult to avoid.

The book is well worthwhile and the correlation of the accumulated knowledge of the tumors of the female pelvic organs in regard to pathology, clinical symptoms and treatment fills a decided need.

J. M. H.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Dr. Herbert Thomas Kelly (Fellow) and Dr. J. T. Beardwood, Jr. (Fellow), Philadelphia, Pa.—one book, "Simplified Diabetic Management."

Dr. Thurman D. Kitchin (Fellow), Wake Forest, N. C.—one book, "The Doctor and Citizenship."

Acknowledgment is also made of the receipt of reprints from the following:

Dr. J. Reid Broderick (Fellow), Savannah, Ga.—1 reprint;
Dr. Alvin G. Foord (Fellow), Pasadena, Calif.—12 reprints;
Dr. W. E. R. Schottstaedt (Fellow), Fresno, Calif.—2 reprints;
Dr. John W. Shuman (Fellow), Los Angeles, Calif.—1 reprint;
Dr. Ramon M. Suarez (Fellow), San Juan, Puerto Rico—3 reprints;
Dr. Willard J. Davies (Associate), Rockville Center, N. Y.—1 reprint.

Dr. Julius H. Comroe, Sr. (Fellow), York, Pa., has been elected to membership upon the Scientific Advisory Board of the American Medical Editors' and Authors' Association, to serve one year, beginning January 1, 1935. Dr. Dean Lewis, Baltimore, Md., has been elected President.

Dr. Henry K. Taylor (Fellow), has been appointed to the teaching staff of the New York University for the academic year 1934 to 1935 as Instructor in Radiology by the Council of that University.

The Southeastern Surgical Congress, through its Secretary, Dr. B. T. Beasley, announces the Sixth Annual Assembly of the Congress, which will be held in Jacksonville, Fla., March 11, 12 and 13, 1935. The Congress has met previously in Atlanta, Birmingham and Nashville. The States composing the Congress are: Alabama, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee and Virginia. Many distinguished surgeons will appear on the program, which will be completed about February 15, 1935. Interested physicians may address Dr. B. T. Beasley, Secretary-Treasurer, 1019 Doctors Bldg., Atlanta, Ga.

The Los Angeles County Heart Association held its Third Annual Symposium on Heart Disease on December 6 and 7, 1934. Dr. A. S. Granger (Fellow) and Dr. William H. Leake (Fellow) are President and Secretary-Treasurer, respectively. The following Fellows of the College contributed to the program:

Dr. E. Richmond Ware	Dr. A. S. Granger	Dr. Roy Thomas
Dr. Willard J. Stone	Dr. Newton Evans	Dr. F. M. Pottenger
Dr. Egerton Crispin	Dr. D. D. Comstock	Dr. Donald J. Frick
Dr. John C. Ruddock	Dr. B. O. Raulston	Dr. Harold H. Smith
Dr. William H. Leake	Dr. Wm. C. Boeck	
Dr. Arthur M. Hoffman	Dr. R. Manning Clarke	

Dr. William Gerry Morgan (Fellow and Secretary-General of the College), Washington, D. C., was named by the Commissioners of the District of Columbia to head a committee for the selection of a new Health Officer for the District of

Columbia. The Committee laid down 15 requisite qualifications for candidates, and has thoroughly investigated the best nominees. The position pays $7,000.00 per annum, and it is expected the candidate will have been elected by the time this announcement is printed.

Elections to the College

At a regular meeting of the Board of Regents of the American College of Physicians at the headquarters in Philadelphia, December 16, 1934, the following elections to Fellowship and Associateship were made. After each candidate's name, "1" indicates the name of the proposer, "2" indicates the name of the seconder, and "3" indicates the name of the endorser.

Elections to Fellowship

George Albert Alden, M.C., U. S. N., Washington, D. C.
(1) P. F. Dickens
(2) Lewis H. Roddis
(3) P. S. Rossiter

George E. Baxter, Chicago, Ill.
(1) N. S. Davis, III
(2) Charles A. Elliott
(3) James G. Carr

A. Lee Briskman, Colorado Springs, Colo.
(1) G. Burton Gilbert
(2) John A. Sevier
(3) Gerald B. Webb

Albert W. Bromer, New York, N. Y.
(1) Thomas M. McMillan
(2) Charles C. Wolferth
(3) William D. Stroud

Michael A. Burns, Philadelphia, Pa.
(1) Edward A. Strecker
(2) Edward Weiss
(3) E. J. G. Beardsley

Horace W. Carle, St. Joseph, Mo.
(1) L. H. Fuson
(2) P. T. Bohan
(3) A. C. Griffith

Fred Ellsworth Clow, Wolfeboro, N. H.
(1) Harry T. French
(2) H. W. N. Bennett
(3) Robert B. Kerr

Sterling Smith Cook, M.C., U. S. N., Washington, D. C.
(1) O. J. Mink
(2) Louis H. Roddis
(3) P. S. Rossiter

Austin Clifford Davis, Rochester, Minn.
(1) W. A. Plummer
(2) George E. Brown
(3) E. L. Tuohy

John J. Dumphy, Worcester, Mass.
(1) Peter A. Colberg
(2) George M. Albee
(3) William B. Breed

Maurice F. Dwyer, Seattle, Wash.
(1) Lester J. Palmer
(2) G. A. Dowling
(3) Frederick Epplen

Mary Hoskins Easby, Philadelphia, Pa.
(1) James E. Talley
(2) Joseph T. Beardwood, Jr.
(3) William D. Stroud and E. J. G. Beardsley

Carl Edgar Ervin, Danville, Pa.
(1) Alfred Stengel
(2) O. H. Perry Pepper
(3) Geo. Morris Piersol

Hugh Allan Farris, St. John, New Brunswick, Can.
(1) W. E. Ogden
(2) Jabez H. Elliott
(3) D. Sclater Lewis

Grant O. Favorite, Philadelphia, Pa.
(1) E. Roland Snader, Jr.
(2) S. W. Sappington
(3) E. J. G. Beardsley

Russell Allen Flack, La Fayette, Ind.
(1) R. D. Bayley
(2) M. M. Lairy
(3) Robert M. Moore

Alvin George Foord, Pasadena, Calif.
(1) Willard J. Stone
(2) F. M. Pottenger
(3) Egerton Crispin

Leonard H. Fredricks, Bismarck, N. D.
(1) H. A. Brandes
(2) Paul H. Rowe
(3) Julius O. Arnson

James Jackson Gable, Norman, Okla.
(1) Tom Lowry
(2) Hugh Jeter
(3) Lea. A. Riely

Amos Carvel Gipson, Gadsden, Ala.
(1) C. C. McLean
(2) Seale Harris
(3) James S. McLester

A. Allen Goldbloom, New York, N. Y.
(1) I. W. Held
(2) Linn J. Boyd and Harlow Brooks
(3) James Alex. Miller and Robert A. Cooke

David Greer, Houston, Texas
(1) M. L. Graves
(2) Moise D. Levy
(3) C. T. Stone

George Tryon Harding, Columbus, Ohio
(1) John Dudley Dunham
(2) E. F. McCampbell
(3) A. B. Brower

William Walter Hargrave, M.C., U. S. N., Washington, D. C.
(1) P. F. Dickens

(2) Walter A. Bloedorn
(3) P. S. Rossiter

Marion Douglas Hargrove, Shreveport, La.
(1) W. S. Kerlin
(2) Dean Hume Duncan
(3) J. E. Knighton

Gordon Hastings, Little Rock, Ark.
(1) F. O. Mahony
(2) H. T. Smith
(3) Oliver C. Melson

Ivan Hekimian, Buffalo, N. Y.
(1) Carroll J. Roberts
(2) Nelson G. Russell
(3) Allen A. Jones

Wybren Hiemstra, Missoula, Mont.
(1) Allen Richard Foss
(2) Harold W. Gregg
(3) Louis H. Fligman

Herbert Thomas Kelly, Philadelphia, Pa.
(1) James E. Talley
(2) Joseph T. Beardwood, Jr.
(3) E. J. G. Beardsley

Dunne Wilson Kirby, Philadelphia, Pa.
(1) G. Harlan Wells
(2) Donald R. Ferguson
(3) Geo. Morris Piersol and E. J. G. Beardsley

Louis I. Kramer, Providence, R. I.
(1) Guy W. Wells
(2) Charles F. Gormly
(3) Alex. M. Burgess

Eugene Markley Landis, Philadelphia, Pa.
(1) T. Grier Miller
(2) Charles C. Wolferth
(3) O. H. Perry Pepper and E. J. G. Beardsley

Lowell Lefferts Lane, Philadelphia, Pa.
(1) E. Roland Snader, Jr.
(2) Donald R. Ferguson
(3) E. J. G. Beardsley

Roy John Leutsker, M.C., U. S. N., San Diego, Calif.
(1) Otis Burgess Spalding
(2) W. A. Vogelsang
(3) P. S. Rossiter

Dean W. Marquis, East Orange, N. J.
(1) Harvey M. Ewing
(2) John W. Gray
(3) Clarence L. Andrews

Alexis Tice Mays, Brooklyn, N. Y.
(1) A. F. R. Andresen
(2) Eugene S. Dalton
(3) Luther F. Warren and Robert A. Cooke

Samuel James McClendon, San Diego, Calif.
(1) Lyell Cary Kinney
(2) Clair L. Stealy
(3) Egerton Crispin

William Patton McDowell, Norfolk, Va.
(1) C. L. Harrell
(2) Walter B. Martin
(3) J. Morrison Hutcheson

Ralph James McMahon, Endicott, N. Y.
(1) H. B. Marvin
(2) James Herbert Donnelly
(3) Robert A. Cooke

Oliver J. Menard, Springfield, Mass.
(1) Lewis M. Hurxthal
(2) Frank N. Allan
(3) Roger I. Lee

Clarence Dewey Moll, Detroit, Mich.
(1) Henry R. Carstens
(2) Alpheus F. Jennings
(3) James D. Bruce

Bradford James Murphey, Colorado Springs, Colo.
(1) G. Burton Gilbert
(2) John A. Sevier
(3) Gerald B. Webb

Sydney Nussbaum, Brooklyn, N. Y.
(1) Philip I. Nash
(2) Judson P. Pendleton
(3) Luther F. Warren and Robert A. Cooke

Marjorie E. Reed, Plymouth, Pa.
(1) G. E. Baker
(2) Edward I. Wolfe
(3) E. J. G. Beardsley

Floyd Leslie Rogers, Lincoln, Nebr.
(1) Geo. W. Covey
(2) A. L. Smith
(3) Adolph Sachs

Edward Rose, Philadelphia, Pa.
(1) T. Grier Miller
(2) Richard A. Kern
(3) O. H. Perry Pepper and E. J. G. Beardsley

Howard A. Rusk, St. Louis, Mo.
(1) Walter Baumgarten
(2) Elsworth S. Smith
(3) A. C. Griffith

Harold Rypins, Albany, N. Y.
(1) Willard C. Rappleye
(2) Luther F. Warren
(3) Wm. Gerry Morgan and Robert A. Cooke

George A. Sheehan, Brooklyn, N. Y.
(1) Tasker Howard
(2) A. F. R. Andresen
(3) Luther F. Warren and Robert A. Cooke

James Joseph Short, New York, N. Y.
(1) Milton A. Bridges
(2) Walter G. Lough
(3) Robert A. Cooke

Neuton S. Stern, Memphis, Tenn.
(1) J. B. McElroy

(2) Otis S. Warr
(3) J. Owsley Manier

John Augustin Sweeney, Philadelphia, Pa.
(1) Joseph C. Doane
(2) Arthur C. Morgan
(3) E. J. G. Beardsley

Charles William Warren, Rochester, N. Y.
(1) William S. McCann
(2) Charles B. F. Gibbs
(3) Allen A. Jones

Harvey Middelton Watkins, Polk, Pa.
(1) W. H. Mayer
(2) A. H. Stewart
(3) E. Bosworth McCready

Ernest S. Wegner, Lincoln, Nebr.
(1) Arthur L. Smith
(2) Geo. W. Covey
(3) Adolph Sachs

August A. Werner, St. Louis, Mo.
(1) Charles Hugh Neilson
(2) Augustus P. Munsch
(3) David Barr

James Alfred Wilson, Meriden, Conn.
(1) Thomas P. Murdock
(2) Cole B. Gibson
(3) Henry F. Stoll

Charles Benjamin Wright, Minneapolis, Minn.
(1) Walter L. Bierring
(2) Frank W. Spicer
(3) Edward L. Tuohy

Elections to Associateship

Kenneth Ellmaker Appel, Philadelphia, Pa.
(1) Edward A. Strecker
(2) Richard A. Kern
(3) O. H. Perry Pepper and E. J. G. Beardsley

James B. Berardi, Tuscaloosa, Ala.
(1) James S. McLester
(2) James E. Paullin
(3) Fred Wilkerson

Ernest L. Boylen, Portland, Ore.
(1) Homer P. Rush
(2) John H. Fitzgibbon
(3) T. Homer Coffen

Irving Brotman, Washington, D. C.
(1) Walter Freeman
(2) Tomás Cajigas
(3) Wallace M. Yater

Paul Douglas Camp, Richmond, Va.
(1) Dean B. Cole
(2) R. Finley Gayle
(3) J. Morrison Hutcheson

T. Nelson Carey, Baltimore, Md.
(1) Maurice C. Pincoffs

(2) Louis Krause
(3) Henry M. Thomas, Jr.

Lyman Bruce Carruthers, Miraj, S. M. C., India
(1) John A. Macgregor
(2) C. M. Crawford
(3) Jabez H. Elliott

John Richard Cavanagh, Washington, D. C.
(1) Lester Neuman
(2) W. F. O'Donnell
(3) Wallace M. Yater

Casimir Joseph Czarnecki, Toledo, Ohio
(1) C. W. Waggoner
(2) John T. Murphy
(3) A. B. Brower

T. Dewey Davis, Richmond, Va.
(1) Charles M. Caravati
(2) Dean B. Cole
(3) J. Morrison Hutcheson

Elbert DeCoursey, M.C., U. S. A., Ancon, Canal Zone
(1) Lawrence Getz
(2) Lewis B. Bates
(3) Wm. M. James

Frederic Griffin Dorwart, Muskogee, Okla.
(1) L. J. Moorman
(2) John E. Heatley
(3) Lea. A. Riely

Charles Hilbert Drenckhahn, Rochester, Minn.
(1) E. V. Allen
(2) A. B. Rivers
(3) E. L. Tuohy

Thomas Morton Durant, Ann Arbor, Mich.
(1) Cyrus C. Sturgis
(2) Charles L. Brown
(3) James D. Bruce

John Sheldon Eastland, Baltimore, Md.
(1) Maurice C. Pincoffs
(2) Louis Krause
(3) Henry M. Thomas, Jr.

Earl B. Erskine, M.C., U. S. N., Parris Island, S. C.
(1) C. S. Butler
(2) I. W. Jacobs
(3) P. S. Rossiter

Daniel Leo Finucane, Washington, D. C.
(1) J. Winthrop Peabody
(2) William D. Tewksbury
(3) Wallace M. Yater

Luther Irvin Fisher, Bethlehem, Pa.
(1) Francis J. Dever
(2) William D. Stroud
(3) Geo. Morris Piersol

James Hedges Forsee, M.C., U. S. A., Denver, Colo.
(1) E. L. Cook
(2) William C. Pollock
(3) Robert U. Patterson

Richard France, Woodbrook, Baltimore Co., Md.
(1) Thomas R. Brown
(2) Sydney R. Miller
(3) Henry M. Thomas, Jr.

William Freeman, Worcester, Mass.
(1) Erwin C. Miller
(2) G. M. Albee
(3) Roger I. Lee and William B. Breed

Sanford William French, M.C., U. S. A., Fort Sam Houston, Texas
(3) Robert U. Patterson

Julian Carrel Gant, Melrose, Mass.
(1) Howard B. Sprague
(2) F. Dennette Adams
(3) J. H. Means and William B. Breed

J. Francis Gardiner, Omaha, Nebr.
(1) John R. Kleyla
(2) Maurice C. Howard
(3) Adolph Sachs

William Middendorf Genthner, Brooklyn, N. Y.
(1) A. F. R. Andresen
(2) Frank Bethel Cross
(3) Robert A. Cooke

Warren Monroe Gilbert, Boulder, Colo.
(1) Clough Turrill Burnett
(2) R. W. Arndt
(3) Gerald B. Webb

Stephen A. Graczyk, Buffalo, N. Y.
(1) Carroll J. Roberts
(2) Francis D. Leopold
(3) Allen A. Jones

William Bandy Grayson, Little Rock, Ark.
(1) F. O. Mahony
(2) H. T. Smith
(3) Oliver C. Melson

William Hugh Griffith, Huron, S. D.
(1) John L. Calene
(2) C. F. Morsman
(3) S. Marx White

Lewis Perkins Gundry, Baltimore, Md.
(1) Maurice C. Pincoffs
(2) Louis Krause
(3) Henry M. Thomas, Jr.

Harry Halprin, Caldwell, N. J.
(1) Harvey M. Ewing
(2) Harlow Brooks
(3) Clarence L. Andrews

James Fletcher Hanson, Decatur, Ga.
(1) Hal M. Davison
(2) C. W. Strickler
(3) Russell H. Oppenheimer

Karl J. Henrichsen, Chicago, Ill.
(1) Henry C. Sweany
(2) Frederick Tice
(3) James B. Herrick and James G. Carr

Edgar Schall Henry, Sewickley, Pa.
(1) Joseph H. Barach
(2) Samuel R. Haythorn
(3) E. Bosworth McCready

Henry Finlay Hyndman, Wichita, Kan.
(1) Thomas T. Holt
(2) Harold W. Palmer
(3) J. H. Musser

Harry Julius Johnson, New York, N. Y.
(1) Milton A. Bridges
(2) J. Russell Twiss
(3) Robert A. Cooke

W. Floyd Keller, Oklahoma City, Okla.
(1) L. J. Moorman
(2) John E. Heatley
(3) Lea. A. Riely

Bert Fletcher Keltz, Oklahoma City, Okla.
(1) L. J. Moorman
(2) Arthur B. Chase
(3) Lea. A. Riely

Robert Leonard King, Seattle, Wash.
(1) George Dowling
(2) John Blackford
(3) Frederick Epplen

Frank Hammond Krusen, Philadelphia, Pa.
(1) Edward Weiss
(2) John A. Kolmer
(3) E. J. G. Beardsley

Romeo J. Lajoie, Los Angeles, Calif.
(1) Bertnard Smith
(2) Howard F. West
(3) F. M. Pottenger and Egerton Crispin

Arthur E. Lamb, Brooklyn, N. Y.
(1) Joshua M. Van Cott
(2) Nathan T. Beers
(3) Luther F. Warren and Robert A. Cooke

Louis B. Laplace, Philadelphia, Pa.
(1) Thomas M. McMillan
(2) David Riesman
(3) W. D. Stroud

William Gilmore Leaman, Jr., Philadelphia, Pa.
(1) Robert G. Torrey
(2) Frank W. Burge
(3) E. J. G. Beardsley

George Morris Lewis, New York, N. Y.
(1) J. Homer Cudmore
(2) Leon T. LeWald
(3) Robert A. Cooke

Thomas K. Lewis, Camden, N. J.
(1) E. J. G. Beardsley
(2) Thomas M. Kain
(3) Clarence L. Andrews

James M. Lynch, Panama City, Panama
(1) Lawrence Getz

(2) C. D. Briscoe
(3) Wm. M. James

Paul Bernard Mason, Rochester, Minn.
(1) George E. Brown
(2) E. V. Allen
(3) E. L. Tuohy

William R. Mathews, Shreveport, La.
(1) D. H. Duncan
(2) W. S. Kerlin
(3) J. E. Knighton

Randolph L. McCalla, San Francisco, Calif.
(1) H. Clare Shepardson
(2) William J. Kerr
(3) H. Lisser

Edward McCloskey, Philadelphia, Pa.
(1) Josephus T. Ullom
(2) T. Grier Miller
(3) Geo. Morris Piersol

John McFaul McEachern, Winnipeg, Man., Can.
(1) J. Currie McMillan
(2) J. G. FitzGerald
(3) Fred T. Cadham

Fred John McEwen, Wichita, Kan.
(1) Howard E. Marchbanks
(2) Peter T. Bohan
(3) Thomas T. Holt

Clovis Litle McKibben, Toledo, Ohio
(1) C. W. Waggoner
(2) John T. Murphy
(3) A. B. Brower

Roscoe Frick Millet, Rochester, Minn.
(1) George E. Brown
(2) E. V. Allen
(3) E. L. Tuohy

Philip Wilhelm Morgan, Emporia, Kan.
(1) Peter T. Bohan
(2) A. Morris Ginsberg
(3) Thomas T. Holt

Samuel Morrison, Baltimore, Md.
(1) Julius Friedenwald
(2) Theodore H. Morrison
(3) Henry M. Thomas, Jr.

Carlisle Morse, Louisville, Ky.
(1) John Walker Moore
(2) J. Murray Kinsman
(3) E. B. Bradley

Charles Scott Mudgett, M.C., U. S. A., Fort Devens, Mass.
(1) John T. Aydelotte
(2) C. H. Beecher
(3) Robert U. Patterson

Bert Ernest Mulvey, Oklahoma City, Okla.
(1) Wann Langston
(2) John E. Heatley
(3) Lea. A. Riely

Jesse Carl Painter, Dubuque, Iowa
(1) John H. Peck
(2) C. B. Luginbuhl
(3) Walter L. Bierring

Arthur Douglas Parker, Norfolk, Va.
(1) C. L. Harrell
(2) Walter B. Martin
(3) J. Morrison Hutcheson

Herman Richard Parker, Greensboro, N. C.
(1) Frederick R. Taylor
(2) P. W. Flagge
(3) C. H. Cocke

H. Raymond Peters, Baltimore, Md.
(1) Louis Krause
(2) Thomas P. Sprunt
(3) M. C. Pincoffs and Henry Thomas, Jr.

Joseph A. Pollia, Los Angeles, Calif.
(1) John V. Barrow
(2) Samuel M. Alter
(3) Egerton Crispin

Joseph W. Post, Philadelphia, Pa.
(1) Frank W. Burge
(2) Edward L. Bortz
(3) Geo. Morris Piersol

Louis Elwood Prickman, Rochester, Minn.
(1) F. W. Gaarde
(2) C. K. Maytum
(3) E. L. Tuohy

William Kendrick Purks, Vicksburg, Miss.
(1) W. N. Jenkins
(2) Felix J. Underwood
(3) G. W. F. Rembert

John A. Reisinger, Philadelphia, Pa.
(1) Alfred Stengel
(2) O. H. Perry Pepper
(3) Wm. D. Stroud

Anthony J. Rejent, Toledo, Ohio
(1) C. W. Waggoner
(2) L. A. Levison
(3) A. B. Brower

Russell Lowell Sands, Santa Monica, Calif.
(1) John V. Barrow
(2) Walter Wessels
(3) Egerton Crispin

Leon Schiff, Cincinnati, Ohio
(1) H. B. Weiss
(2) Henry Wald Bettmann
(3) A. B. Brower

Jesse Bedford Shelmire, Dallas, Texas
(1) C. Frank Brown
(2) D. W. Carter, Jr.
(3) C. T. Stone

Isaac Judah Silverman, Washington, D. C.
(1) W. A. Bloedorn

(2) C. B. Conklin
(3) Wallace M. Yater

Stanley David Simon, Cincinnati, Ohio
(1) H. B. Weiss
(2) Henry Wald Bettmann
(3) A. B. Brower

Edwin J. Simons, Swanville, Minn.
(1) J. A. Myers
(2) H. A. Burns
(3) S. Marx White

Francis Harper Sleeper, Worcester, Mass.
(1) Helmuth Ulrich
(2) Herman C. Petterson
(3) William B. Breed

Louis Sommer, Cincinnati, Ohio
(1) Henry Wald Bettmann
(2) H. B. Weiss
(3) A. B. Brower

Will Cook Spain, New York, N. Y.
(1) Milton A. Bridges
(2) J. Russell Twiss
(3) Robert A. Cooke

Charles Henry Sprague, Des Moines, Iowa
(1) H. A. Collins
(2) Edward W. Anderson
(3) Tom B. Throckmorton

Thomas Autin Starkey, Rochester, Minn.
(1) George E. Brown
(2) E. V. Allen
(3) E. L. Tuohy

Gilbert Miller Stevenson, Pedro Miguel, C. Z.
(1) C. D. Briscoe
(2) Tomas Guardia
(3) Wm. M. James

Charles Roberts Thomas, Chattanooga, Tenn.
(1) Franklin B. Bogart
(2) Wm. D. Anderson
(3) J. O. Manier

Edwin T. Thorsness, Casper, Wyo.
(1) J. C. Kamp
(2) C. F. Morsman
(3) Adolph Sachs

Pat Alexander Tuckwiller, Charleston, W. Va.
(1) Martin L. Bonar
(2) R. D. Roller, Jr.
(3) John N. Simpson

Leon Unger, Chicago, Ill.
(1) A. A. Goldsmith
(2) Frederick Tice
(3) James G. Carr

Charles Edgar Virden, Kansas City, Mo.
(1) Harry L. Jones
(2) A. Morris Ginsberg
(3) A. C. Griffith

Harry Walker, Richmond, Va.
(1) R. Finley Gayle, Jr.
(2) Wm. B. Porter
(3) J. Morrison Hutcheson
Jacob Werne, Jamaica, L. I., N. Y.
(1) Morris Weisberg
(2) Harlow Brooks
(3) Luther F. Warren and Robert A. Cooke
Joseph H. Whiteley, M.C., U. S. A., Washington, D. C.
(3) Robert U. Patterson
Willard Ralph Wirth, New Orleans, La.
(1) I. I. Lemann
(2) Randolph Lyons
(3) J. H. Musser and J. E. Knighton
Burbridge Scott Yancey, Harrisonburg, Va.
(1) H. B. Mulholland
(2) J. Edwin Wood, Jr.
(3) J. Morrison Hutcheson